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L13: Entry 12 of 23 File: USPT Nov 14, 2000

DOCUMENT-IDENTIFIER: US 6147109 A
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TITLE: Upregulation of Type III endothelial cell Nitric Oxide Synthase by HMG-CoA reductase inhibitors

Brief Summary Text (4):
Nitric oxide (NO) has been recognized as an unusual messenger molecule with many physiologic roles, in the cardiovascular, neurologic and immune systems (Griffith, T M et al., J Am Coll Cardiol, 1988, 12:797-806). It mediates blood vessel relaxation, neurotransmission and pathogen suppression. NO is produced from the guanidino nitrogen of L-arginine by NO Synthase (Moncada, S and Higgs, E A, Eur J Clin Invest, 1991, 21(4):361-374). In mammals, at least three isoenzymes of NO Synthase have been identified. Two, expressed in neurons (NNOS) and endothelial cells (Type III-ecNOS), are calcium-dependent, whereas the third is calcium-independent and is expressed by macrophages and other cells after induction with cytokines (Type I-iNOS) (Bredt, D S and Snyder, S H, Proc Natl Acad Sci USA, 1990, 87:682-685, Janssens, S P et al., J Biol Chem, 1992, 267:22964, Lyons, C R et al., J Biol Chem, 1992, 267:6370-6374). The various physiological and pathological effects of NO can be explained by its reactivity and different routes of formation and metabolism.

Drawing Description Text (10):
FIG. 10. Neurological deficit score of wild-type SV-129 mice with and without treatment with simvastatin.

Detailed Description Text (8):
One important embodiment of the invention is treatment of ischemic stroke. Ischemic stroke (ischemic cerebral infarction) is an acute neurologic injury that results from a decrease in the blood flow involving the blood vessels of the brain. Ischemic stroke is divided into two broad categories, thrombotic and embolic.

Detailed Description Text (9):
A surprising finding was made in connection with the treatment of ischemic stroke. In particular, it was discovered that treatment according to the invention can reduce the brain injury that follows an ischemic stroke. Brain injury reduction, as demonstrated in the examples below, can be measured by determining a reduction in infarct size in the treated versus the control groups. Likewise, functional tests measuring neurological deficits provided further evidence of reduction in brain injury in the treated animals versus the controls. Cerebral blood flow also was better in the treated animals versus the controls. Thus, in the various accepted models of brain injury following stroke, a positive effect was observed in the treated animals versus the control animals. It is believed that all of the foregoing positive results are attributable to the upregulation of endothelial cell Nitric Oxide Synthase activity, which is believed demonstrated in the examples below.

Detailed Description Text (36):
Examples of categories of pharmaceutical agents include: adrenergic agent; adrenocortical steroid; adrenocortical suppressant; alcohol deterrent; aldosterone antagonist; amino acid; ammonia detoxicant; anabolic; analeptic; analgesic; androgen; anesthesia, adjunct to; anesthetic; anorectic; antagonist; anterior pituitary suppressant; anthelmintic; anti-acne agent; anti-adrenergic; anti-allergic; anti-amebic; anti-androgen; anti-anemic; anti-anginal; anti-anxiety; anti-arthritic; anti-asthmatic; anti-atherosclerotic; antibacterial; anticholelithic; anticholelithogenic; anticholinergic; anticoagulant; anticoccidal; anticonvulsant; antidepressant; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti-epileptic; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent;

antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; anti-infective; anti-infective, topical; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiobessional agent; antiparasitic; antiparkinsonian; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy; antiprotozoal; antipruritic; antipsychotic; antirheumatic; antischistosomal; antiseborrheic; antisecretory; antispasmodic; antithrombotic; antitussive; anti-ulcerative; anti-urolithic; antiviral; appetite suppressant; benign prostatic hyperplasia therapy agent; blood glucose regulator; bone resorption inhibitor; bronchodilator; carbonic anhydrase inhibitor; cardiac depressant; cardioprotectant; cardiotonic; cardiovascular agent; choleretic; cholinergic; cholinergic agonist; cholinesterase deactivator; coccidiostat; cognition adjuvant; cognition enhancer; depressant; diagnostic aid; diuretic; dopaminergic agent; ectoparasiticide; emetic; enzyme inhibitor; estrogen; fibrinolytic; fluorescent agent; free oxygen radical scavenger; gastrointestinal motility effector; glucocorticoid; gonad-stimulating principle; hair growth stimulant; hemostatic; histamine H2 receptor antagonists; hormone; hypocholesterolemic; hypoglycemic; hypolipidemic; hypotensive; imaging agent; immunizing agent; immunomodulator; immunoregulator; immunostimulant; immunosuppressant; impotence therapy adjunct; inhibitor; keratolytic; LNRII agonist; liver disorder treatment; luteolysin; memory adjuvant; mental performance enhancer; mood regulator; mucolytic; mucosal protective agent; mydriatic; nasal decongestant; neuromuscular blocking agent; neuroprotective; NMDA antagonist; non-hormonal sterol derivative; oxytocic; plasminogen activator; platelet activating factor antagonist; platelet aggregation inhibitor; post-stroke and post-head trauma treatment; potentiator; progestin; prostaglandin; prostate growth inhibitor; prothyrotropin; psychotropic; pulmonary surface; radioactive agent; regulator; relaxant; repartitioning agent; scabicide; sclerosing agent; sedative; sedative-hypnotic; selective adenosine A1 antagonist; serotonin antagonist; serotonin inhibitor; serotonin receptor antagonist; steroid; stimulant; suppressant; symptomatic multiple sclerosis; synergist; thyroid hormone; thyroid inhibitor; thyromimetic; tranquilizer; treatment of amyotrophic lateral sclerosis; treatment of cerebral ischemia; treatment of Paget's disease; treatment of unstable angina; uricosuric;

Detailed Description Text (107):
Adult male (18-20 g) wildtype SV-129 mice (Taconic farm, Germantown, N.Y.) and ecNOS mutant mice (Huang, P L et al., Nature, 1995, 377:239-242.) were subcutaneously-injected with 0.2, 2, or 20 mg of activated simvastatin per kg body weight or saline (control) once daily for 14 days. Ischemia was produced by occluding the left middle cerebral artery (MCA) with a coated 8.0 nylon monofilament under anesthesia as described (Huang, Z et al., J Cereb Blood Flow Metab, 1996, 16:981-987, Huang, Z et al., Science, 1994, 20 265:1883-1885, Hara, H et al., J Cereb Blood Flow Metab, 1997, 1:515-526). Arterial blood pressure, heart rate, arterial oxygen pressure, and partial pressure of carbon dioxide were monitored as described (Huang, Z et al., J Cereb Blood Flow Metab, 1996, 16:981-987, Huang, Z et al., Science, 1994, 265:1883-1885, Hara, H et al., J Cereb Blood Flow Metab, 1997, 1:515-526). The filaments were withdrawn after 2 hours and after 24 h, mice were either sacrificed or tested for neurological deficits using a well-established, standardized, observer-blinded protocol as described (Huang, Z et al., J Cereb Blood Flow Metab, 1996, 16:981-987, Huang, Z et al., Science, 1994, 265:1883-1885, Hara, H et al., J Cereb Blood Flow Metab, 1997, 1:515-526). The motor deficit score range from 0 (no deficit) to 2 (complete deficit).

Detailed Description Text (139):
Endothelium-derived NO protects against ischemic cerebral injury (Huang, Z et al., J Cereb Blood Flow Metab, 1996, 16:981-987). Therefore we examined, wether the observed upregulation of ecNOS by simvastatin in vivo has beneficial effects on cerebral infarct size. Following treatment for 14 days with 2 mg/kg of simvastatin, cerebral ischemia was produced by occluding the left middle cerebral artery for 2 hours. After 22 hours of reperfusion, mice were tested for neurological deficits using a well-established, standardized, observer-blinded protocol (FIG. 10). The neurological motor deficit score improved in simvastatin-treated mice (n=18) by almost 2-fold compared to that of controls (n=12) (0.8.+-.0.2 vs. 1.7.+-.0.2, p<0.01).

Detailed Description Text (140):
Simvastatin-treated wild-type mice (n=1 8) had 25% smaller cerebral infarct sizes compared to untreated animals (73.8.+-.8.5 mm3 vs. 100.7.+-.7.3 mm3, n=12, p<0.05) (FIG. 11A). This effect was concentration-dependent (0.2, 2, 20 mg/kg simvastatin), persisted for up to 3 days, and also occurred with lovastatin treatment, albeit at higher relative concentrations (data not shown). Furthermore, simvastatin increase

cerebral blood flow by 23% and 35% over basal values at concentrations of 2 mg/kg and 20 mg/kg, respectively (n=8, p<0.05 for both). These findings suggest, that simvastatin decreases cerebral infarct size and neurological deficits.

Detailed Description Text (157):
FIG. 10. Neurological deficit score of wild-type SV-129 mice after treatment with simvastatin (Sim, 2 mg/kg, s.c., 14 days) compared to mice injected with saline (Control) (n=12, p<0.01).

Other Reference Publication (34):
Laufs et al., "Post-transcriptional Regulation of Endothelial Nitric Oxide Synthase mRNA Stability by Rho GTPase," The Journal of Biological Chemistry, vol. 273, NO. 37, pp. 24266-24271, Sep. 11, 1998.

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SEARCH REQUEST FORM

2707 3

Examiner # (Mandatory): 76707 Requester's Full Name: S Turner

Art Unit 1644 Location (Bldg/Room#): CM1 8A12 Phone (circle 305 306 308) 0056

Serial Number: 09/184,572 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention _____

Inventors (please provide full names): _____

Earliest Priority Date: 11-2-98

Keywords (include any known synonyms registry numbers, explanation of initialisms):

Authorsearch
Mckerracher Lisa
Lehmann Maxime
Fournier Alyson

Point of Contact:
Mary Hale
Technical Info. Specialist
CM1 12D16 Tel: 308-4258

Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

Rho antagonists and (nerve neuron neurite) outgrowth

ADP-ribosyl transferase C3 and (↓) outgrowth

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1515

18.90
6.20
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_____ In-house sequence systems (list)
_____ Dialog
_____ Dr. Link
_____ Westlaw
_____ Other (specify)

L41 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2000 BIOSIS
1999:80468 Document No.: PREV199900080468. Regeneration of adult rat retinal ganglion cell (RGC) axons after microlesion and inactivation of the GTPase
RHO by treatment with C3 enzyme. Selles-Navarro, I.; **Fournier, A.**; Dergham, P.; **Lehmann, M.**; **McKerracher, L.**. Dep. Pathol. Biol. Cell., Univ. Montral, C.P. 6128, Succursale Centre-ville, Montreal, PQ H3C 3J7 Canada. Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 1560. Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 2 Los Angeles, California, USA November 7-12, 1998 ISSN: 0190-5295. Language: English.

L41 ANSWER 3 OF 3 BIOSIS COPYRIGHT 2000 BIOSIS
1998:21076 Document No.: PREV199800021076. Role of Rho in regulating inhibition of neurite growth by myelin-associated glycoprotein (MAG. **Lehmann, M.**; **Fournier, A.**; Leclerc, N.; Tigyi, G.; **McKerracher, L.**. Dep. Pathol., Univ. Montreal, CP 6128, Montreal, PQ H3C 3J7 Canada. Molecular Biology of the Cell, (Nov., 1997) Vol. 8, No.
SUPPL., pp. 284A. Meeting Info.: 37th Annual Meeting of the American Society for Cell Biology Washington, D.C., USA December 13-17, 1997 American Society for Cell Biology. ISSN: 1059-1524. Language: English.

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=> fil reg

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	110.67	455.42

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TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Structure search limits have been increased. See HELP SLIMIT for details.

=> e "adp-ribosyl transferase"/cn

E1	1	ADP-RIBOSYL CYCLASE/CYCLIC ADP-RIBOSE HYDROLASE (RAT ISLETS OF LANGERHANS)/CN
E2	1	ADP-RIBOSYL PROTEIN LYASE/CN
E3	0 -->	ADP-RIBOSYL TRANSFERASE/CN
E4	1	ADP-RIBOSYLACTIN HYDROLASE/CN
E5	1	ADP-RIBOSYLARGININE GLYCOHYDROLASE/CN
E6	1	ADP-RIBOSYLARGININE HYDROLASE/CN
E7	1	ADP-RIBOSYLARGININE HYDROLASE (HUMAN BRAIN CLONE 4)/CN
E8	1	ADP-RIBOSYLARGININE HYDROLASE (MOUSE BRAIN)/CN
E9	1	ADP-RIBOSYLATION FACTOR (ARABIDOPSIS THALIANA GENE AT2G15310)/CN
E10	1	ADP-RIBOSYLATION FACTOR (ARABIDOPSIS THALIANA GENE AT2G18390)/CN
E11	1	ADP-RIBOSYLATION FACTOR (ARABIDOPSIS THALIANA STRAIN COLUMBIA)/CN
E12	1	ADP-RIBOSYLATION FACTOR (DUGESIA JAPONICA STRAIN GI)/CN

=> e

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E13             1     ADP-RIBOSYLATION FACTOR (PLASMODIUM FALCIPARUM)/CN
E14             1     ADP-RIBOSYLATION FACTOR (SACCHAROMYCES CEREVISIAE CLONE
2I12
                       GENE ARF2)/CN
E15             1     ADP-RIBOSYLATION FACTOR 1 (ARABIDOPSIS THALIANA GENE
AT2G471
                      70)/CN
E16             1     ADP-RIBOSYLATION FACTOR 1 (MOUSE ADP RIBOSIDATION)/CN
E17             1     ADP-RIBOSYLATION FACTOR 1 (RAT)/CN
E18             1     ADP-RIBOSYLATION FACTOR 1 (SCHIZOSACCHAROMYCES POMBE CLONE
9
                      1.2-11 GENE ARF1)/CN
E19             1     ADP-RIBOSYLATION FACTOR 1 (XENOPUS LAEVIS)/CN
E20             1     ADP-RIBOSYLATION FACTOR 2 (MOUSE ADP RIBOSIDATION)/CN
E21             1     ADP-RIBOSYLATION FACTOR 2 (OX CLONE 1)/CN
E22             1     ADP-RIBOSYLATION FACTOR 2 (RAT)/CN
E23             1     ADP-RIBOSYLATION FACTOR 2 LIPOPROTEIN (CATTLE)/CN
E24             1     ADP-RIBOSYLATION FACTOR 3 (MOUSE ADP RIBOSIDATION)/CN

=> e

E25             1     ADP-RIBOSYLATION FACTOR 3 (RAT)/CN
E26             1     ADP-RIBOSYLATION FACTOR 4 (HUMAN CLONE PAC-10/4 GENE
ARF4)/C
                      N
E27             1     ADP-RIBOSYLATION FACTOR 4 (MOUSE ADP RIBOSIDATION)/CN
E28             1     ADP-RIBOSYLATION FACTOR 4 (RAT)/CN
E29             1     ADP-RIBOSYLATION FACTOR 5 (HUMAN CLONE 161C9 GENE ARF5
REDUC
                      ED)/CN
E30             1     ADP-RIBOSYLATION FACTOR 5 (MOUSE ADP RIBOSIDATION)/CN
E31             1     ADP-RIBOSYLATION FACTOR 5 (RAT)/CN
E32             1     ADP-RIBOSYLATION FACTOR 6 (MOUSE ADP RIBOSIDATION)/CN
E33             1     ADP-RIBOSYLATION FACTOR 6 (RAT)/CN
E34             1     ADP-RIBOSYLATION FACTOR ARF 2 (SACCHAROMYCES CEREVISIAE
CLON
                      E 2I12 CHROMOSOME IV GENE ARF2)/CN
E35             1     ADP-RIBOSYLATION FACTOR ARF-4 (RAT)/CN
E36             1     ADP-RIBOSYLATION FACTOR ARF1 (PLASMODIUM FALCIPARUM GENE
PAR
                      F1)/CN

=> e

E37             1     ADP-RIBOSYLATION FACTOR-DIRECTED GTPASE ACTIVATING PROTEIN
(
                      MUS MUSCULUS GENE SHAG1 ISOFORM A)/CN
E38             1     ADP-RIBOSYLATION FACTOR-DIRECTED GTPASE ACTIVATING PROTEIN
(
                      MUS MUSCULUS GENE SHAG1 ISOFORM B)/CN
E39             1     ADP-RIBOSYLATION FACTOR-LIKE 4 (MOUSE GENE ARL4)/CN
E40             1     ADP-RIBOSYLATION FACTOR-LIKE PROTEIN 1 (SACCHAROMYCES
CEREVI
                      SIAE GENE ARL1)/CN
E41             1     ADP-RIBOSYLATION FACTOR-LIKE PROTEIN 3 (MUS MUSCULUS GENE
AR
                      L3)/CN
E42             1     ADP-RIBOSYLATION FACTOR-LIKE PROTEIN 7 (HUMAN TESTIS GENE
AR
                      L7)/CN
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E43           1     ADP-RIBOSYLATION-LIKE FACTOR 6 PROTEIN (MOUSE J2E CELL
GENE
                    ARL6)/CN
E44           1     ADP-RIBOSYLGLYCOHYDROLAS E (AQUIFEX AEOLICUS GENE DRAG)/CN
E45           1     ADP-RIBOSYLGLYCOHYDROLAS E (DEINOCOCCUS RADIODURANS STRAIN
R
                    1 GENE DR1958)/CN
E46           1     ADP-RIBOSYLHISTONE HYDROLASE/CN
E47           1     ADP-RIBOSYLHYDROLASE/CN
E48           1     ADP-RIBOSYLPROTEIN HYDROLASE/CN

=> s adp(l)ribosyl(l)transferase

          530 ADP
          436 RIBOSYL
        19373 TRANSFERASE
            4 TRANSFERASES
        19373 TRANSFERASE
                (TRANSFERASE OR TRANSFERASES)
L1         37 ADP(L)RIBOSYL(L)TRANSFERASE

=> e rho antagonist/cn 5

E1            1     RHO A-BINDING KINASE/CN
E2            1     RHO A-BINDING KINASE .ALPHA./CN
E3            0 --> RHO ANTAGONIST/CN
E4            1     RHO C/CN
E5            1     RHO GDP DISSOCIATION FACTOR (SACCHAROMYCES CEREVISIAE
CLONE
                    2I12 CHROMOSOME IV)/CN

=> s rho antagonist

          481 RHO
          280 ANTAGONIST
L2          0 RHO ANTAGONIST
                (RHO(W)ANTAGONIST)

=> fil medl,caplus,biosis,embase,wpids;s rho antagonis? and (nerve or neuron
or neurite)

COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
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FULL ESTIMATED COST                                18.90     474.32

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L3 1 FILE MEDLINE
L4 2 FILE CAPLUS
L5 0 FILE BIOSIS
L6 1 FILE EMBASE
L7 0 FILE WPIDS

TOTAL FOR ALL FILES
L8 4 RHO ANTAGONIS? AND (NERVE OR NEURON OR NEURITE)

=> dup rem l8

PROCESSING COMPLETED FOR L8
L9 3 DUP REM L8 (1 DUPLICATE REMOVED)

=> d 1-3 cbib abs;s (l1 or adp ribosyl transferase) and c3 and (nerve or neuron or neurite)

L9 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2000 ACS
1999:311220 Document No. 130:320860 Rho family antagonists and their use to block inhibition of **neurite** outgrowth. McKerracher, Lisa; Lehmann, Maxime (Can.). PCT Int. Appl. WO 9923113 A2 19990514, 47 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-CA1013 19981102. PRIORITY: CA 1997-2214841 19971031.
AB The invention provides for the use of antagonists of Rho, or proteins related to Rho, as therapeutic targets for agents designed to block growth inhibition by myelin or myelin proteins. One embodiment pertains to the use of **Rho antagonists** that foster axon regeneration in the central nervous system. The therapeutic agent or antagonist can be small mols., proteins or peptides, or any agent that binds to Rho or its family members to inactivate this pathway. Embodiments include: the use of the Rho regulatory pathway as a target for **Rho antagonists**; the use of GDP dissocn. inhibitors (GDIs) inhibit the dissocn. of GDP from Rho, and thereby prevent the binding of GTP necessary for the activation of Rho; the use of Rho specific GTPase activating protein (GAPs) as targets for the regulation of Rho activity; the use of agents that promote Rho binding to GDI, and block Rho binding to the plasma membrane are also considered within the scope of this invention; the use of C3 transferase and related toxins such as A and B, with related Rho-inhibitory activity to inactivate Rho and stimulate axon growth; the use of dominant neg. forms of Rho, used to inactivate Rho, to foster axon growth.

L9 ANSWER 2 OF 3 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

1999382285 EMBASE Rho family antagonists and their use to block inhibition of
neurite growth. McKerracher L.; et al.. Expert Opinion on Therapeutic Patents 9/11 (1571-1574) 1999.
Refs: 9.
ISSN: 1354-3776. CODEN: EOTPEG. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Rho, a small GTP binding protein with intrinsic GTPase activity, is known to play a role in convergent signalling pathways which alter cell morphology and motility. This patent presents evidence that antagonism of Rho blocks the **neurite** growth-inhibitor effects of myelin-associated glycoprotein (MAG). These findings may have clinical applications in the stimulation of axonal regeneration following injury within the CNS, and possibly in the treatment of neurodegenerative disorders.

L9 ANSWER 3 OF 3 MEDLINE DUPLICATE 1
2000032782 Document Number: 20032782. Rac regulates phosphorylation of the myosin-II heavy chain, actinomyosin disassembly and cell spreading. van Leeuwen F N; van Delft S; Kain H E; van der Kammen R A; Collard J G. (The Netherlands Cancer Institute, Division of Cell Biology, Amsterdam, The Netherlands.) Nat Cell Biol, (1999 Aug) 1 (4) 242-8. Journal code: DIQ.
ISSN: 1465-7392. Pub. country: ENGLAND: United Kingdom. Language: English.
AB GTPases of the Rho family regulate actinomyosin-based contraction in non-muscle cells. Activation of Rho increases contractility, leading to cell rounding and **neurite** retraction in neuronal cell lines. Activation of Rac promotes cell spreading and interferes with Rho-mediated cell rounding. Here we show that activation of Rac may antagonize Rho by regulating phosphorylation of the myosin-II heavy chain. Stimulation of PC12 cells or N1E-115 neuroblastoma cells with bradykinin induces phosphorylation of threonine residues in the myosin-II heavy chain; this phosphorylation is Ca2+ dependent and regulated by Rac. Both bradykinin-mediated and constitutive activation of Rac promote cell spreading, accompanied by a loss of cortical myosin II. Our results identify the myosin-II heavy chain as a new target of Rac-regulated kinase pathways, and implicate Rac as a **Rho antagonist** during myosin-II-dependent cell-shape changes.

L10 1 FILE MEDLINE
L11 9 FILE CAPLUS
L12 5 FILE BIOSIS
L13 3 FILE EMBASE
L14 1 FILE WPIDS

TOTAL FOR ALL FILES
L15 19 (L1 OR ADP RIBOSYL TRANSFERASE) AND C3 AND (NERVE OR NEURON OR NEURITE)

=> dup rem l15

PROCESSING COMPLETED FOR L15
L16 11 DUP REM L15 (8 DUPLICATES REMOVED)

=> d 1-11 cbib abs;s mckerracher l?/au,in;s lehmann m?/au,in;s fournier a?/au,in

L16 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 1
1999:311220 Document No. 130:320860 Rho family antagonists and their use to block inhibition of **neurite** outgrowth. McKerracher, Lisa; Lehmann, Maxime (Can.). PCT Int. Appl. WO 9923113 A2 19990514, 47 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-CA1013 19981102. PRIORITY: CA 1997-2214841 19971031.

AB The invention provides for the use of antagonists of Rho, or proteins related to Rho, as therapeutic targets for agents designed to block growth inhibition by myelin or myelin proteins. One embodiment pertains to the use of Rho antagonists that foster axon regeneration in the central nervous system. The therapeutic agent or antagonist can be small mols., proteins or peptides, or any agent that binds to Rho or its family members to inactivate this pathway. Embodiments include: the use of the Rho regulatory pathway as a target for Rho antagonists; the use of GDP dissocn. inhibitors (GDIs) inhibit the dissocn. of GDP from Rho, and thereby prevent the binding of GTP necessary for the activation of Rho; the use of Rho specific GTPase activating protein (GAPs) as targets for the regulation of Rho activity; the use of agents that promote Rho binding to GDI, and block Rho binding to the plasma membrane are also considered within the scope of this invention; the use of **C3** transferase and related toxins such as A and B, with related Rho-inhibitory activity to inactivate Rho and stimulate axon growth; the use of dominant neg. forms of Rho, used to inactivate Rho, to foster axon growth.

L16 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2000 ACS
1999:795994 Document No. 132:31744 Gene probes used for genetic profiling in healthcare screening and planning. Roberts, Gareth Wyn (Genostic Pharma Ltd., UK). PCT Int. Appl. WO 9964627 A2 19991216, 745 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1780 19990604. PRIORITY: GB 1998-12099 19980606; GB 1998-13291 19980620; GB 1998-13611 19980624; GB 1998-13835 19980627; GB 1998-14110 19980701; GB 1998-14580 19980707; GB 1998-15438 19980716; GB 1998-15576 19980718; GB 1998-15574 19980718; GB 1998-16085 19980724; GB 1998-16086 19980724; GB 1998-16921 19980805; GB 1998-17097 19980807; GB 1998-17200 19980808; GB 1998-17632 19980814; GB 1998-17943 19980819.

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response.

In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies which comprises of the identification of the core group of genes and their sequence variants required to provide a broad base of clin. prognostic information - "genostics". The "Genostic.RTM." profiling of patients and persons will radically enhance the ability of clinicians, healthcare professionals and other parties to plan and manage healthcare provision and the targeting of appropriate healthcare resources to those deemed most in need. The use of this invention could also lead to a host of new applications for such profiling technologies, such as identification of persons with particular work or environment related risk, selection of applicants for employment, training or specific opportunities or for the enhancing of the planning and organization of health services, education services and social services.

L16 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2000 ACS
1999:795993 Document No. 132:31743 Gene probes used for genetic profiling in healthcare screening and planning. Roberts, Gareth Wyn (Genostic Pharma Limited, UK). PCT Int. Appl. WO 9964626 A2 19991216, 149 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-GB1779 19990604. PRIORITY: GB 1998-12098 19980606; GB 1998-28289 19981223.

AB There is considerable evidence that significant factor underlying the individual variability in response to disease, therapy and prognosis lies in a person's genetic make-up. There have been numerous examples relating that polymorphisms within a given gene can alter the functionality of the protein encoded by that gene thus leading to a variable physiol. response. In order to bring about the integration of genomics into medical practice and enable design and building of a technol. platform which will enable the everyday practice of mol. medicine a way must be invented for the DNA sequence data to be aligned with the identification of genes central to the induction, development, progression and outcome of disease or physiol. states of interest. According to the invention, the no. of genes and their configurations (mutations and polymorphisms) needed to be identified in order to provide crit. clin. information concerning individual prognosis is considerably less than the 100,000 thought to comprise the

human genome. The identification of the identity of the core group of genes enables the invention of a design for genetic profiling technologies.

L16 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2000 ACS
1999:136803 Document No. 130:191899 Rho protein inhibitors for central nervous system axon regeneration. Strittmatter, Stephen M. (Yale University, USA). PCT Int. Appl. WO 9908533 A1 19990225, 45 pp. DESIGNATED STATES: W: AU, CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US16794 19980812. PRIORITY: US 1997-55268 19970813.
AB Therapies for the treatment of a variety of central nervous system injuries including acute or chronic spinal cord injury, traumatic brain injury, and white matter stroke involve the administration of rho protein inhibitors to promote axon regeneration. Local administration is employed in typical embodiments, and this may include injection of a recombinant virus that expresses an inhibitor. In one embodiment, the inhibitor is C. botulinum **C3** exoenzyme or a chimeric C. botulinum C2/**C3** construct expressed in a replication-deficient adeno, adeno-assocd., or herpes virus.

L16 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2000 ACS
1997:686625 Document No. 128:2257 Regulation of dendritic growth and remodeling by Rho, Rac, and Cdc42. Threadgill, Richard; Bobb, Kathryn; Ghosh, Anirvan (Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA). Neuron, 19(3), 625-634 (English) 1997. CODEN: NERNET. ISSN: 0896-6273. Publisher: Cell Press.
AB The acquisition of cell type-specific morphologies is a central feature of neuronal differentiation and has important consequences for nervous system function. To begin to identify the underlying mol. mechanisms, we have explored the role of Rho-related GTPases in the dendritic development of cortical **neurons**. Expression of dominant neg. mutants of Rac or Cdc42, the Rho-inhibitory mol. **C3** transferase, or the GTPase-activating protein RhoGAP p190 causes a marked redn. in the no. of primary dendrites in nonpyramidal (multipolar) **neurons** and in the no. of basal dendrites in **neurons** with pyramidal morphologies. Conversely, the expression of constitutively active mutants of Rho, Rac, or Cdc42 leads to an increase in the no. of primary and basal dendrites. In cortical cultures, as in vivo, dendritic remodeling leads to an apparent transformation from pyramidal to nonpyramidal morphologies over time. Strikingly, this shift in favor of nonpyramidal morphologies is also inhibited by the expression of dominant neg. mutants of Cdc42 and Rac and by RhoGAP p190. These observations indicate that Rho, Rac, and Cdc42 play a central role in dendritic development and suggest that differential activation of Rho-related GTPases may contribute to the generation of morphol. diversity in the developing cortex.

L16 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
1995:500288 Document No. 122:285367 Identification of gangliosides as inhibitors of ADP-ribosyltransferases of pertussis toxin and exoenzyme **C3** from Clostridium botulinum. Hara-Yokoyama, Miki; Hirabayashi, Yoshio; Irie, Fumitoshi; Syuto, Bunei; Moriishi, Kohji; Sugiya, Hiroshi; Furuyama, Shunsuke (Dep. Physiology, Nihon Univ. Sch. Dentistry, Matsudo, Chiba, 271, Japan). J. Biol. Chem., 270(14), 8115-21 (English) 1995.

CODEN: JBCHA3. ISSN: 0021-9258.

AB We have previously reported the presence of an endogenous inhibitory activity in bovine brain for the ADP-ribosylation of GTP-binding proteins catalyzed by pertussis toxin (PT) (Hara-Yokoyama, M., and Furuyama, S. (1989) Biochem. Biophys. Res. Commun. 160, 67-71). In the present study, we identified the inhibitor as a ganglioside. The screening of various gangliosides revealed that GQ1b.alpha. most effectively inhibited the ADP-ribosyltransferase activities of both the holoenzyme and the catalytic subunit of PT. GQ1b.alpha. is a ganglioside newly identified as one of the antigens recognized by the cholinergic **neuron**-specific antibody, anti-Chol-1.alpha. (Hirabayashi, Y., Nakao, T., Irie, F., Whittaker, V. P., Kon, K., and Ando, S. (1992) J. Biol. Chem. 267, 12973-12978). GQ1b.alpha. also inhibited the PT-catalyzed NAD+ glycohydrolysis. Unlike PT activity, the ADP-ribosylation and the NAD+ glycohydrolysis catalyzed by the **C3** exoenzyme from Clostridium botulinum type C were inhibited by GT1b and GQ1b. The ADP-ribosylation catalyzed by either PT or the **C3** exoenzyme was not inhibited by ceramide, galactocerebroside, or sialic acid. In addn. to the inhibitory action of gangliosides on ADP-ribosylation, the importance of gangliosides as regulators of NAD+ metab. is discussed.

L16 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 3

1994:552659 Document No. 121:152659 Morphological effects, rate of incorporation, and the enzymic action of botulinum ADP-ribosyltransferase, known as **C3** exoenzyme, on human neuroblastoma GOTO cells. Kamata, Yoichi; Nishiki, Tei-ichi; Matsumura, Kunihiko; Hiroi, Toyoko; Kozaki, Shunji (College Agriculture, Univ. Osaka Prefecture, Sakai, 593, Japan). Microbiol. Immunol., 38(6), 421-8 (English) 1994. CODEN: MIIMDV. ISSN: 0385-5600.

AB The susceptibility of various lines of cultured cells to **C3** exoenzyme was examd. Human neuroblastoma GOTO cells were most sensitive. The **C3** exoenzyme caused a change in cell shape that involved extension of **neurites**. The exoenzyme evoked the outgrowth of **neurites** from chick ganglion as effectively as **nerve** growth factor, suggesting that **C3** exoenzyme possesses neurotropic activity. Expts. with 125I-labeled enzyme revealed that **C3** exoenzyme was rapidly incorporated into cells but the no. of incorporated enzyme mols. was small. Once **C3** exoenzyme had been incorporated, ADP-ribosylation of the substrate (Rho protein) in GOTO cells occurred immediately and rapidly reached a max. level. However, some of Rho proteins remained unmodified even after induction of the change in morphol. These findings suggest that ADP-ribosylation by **C3** exoenzyme is directly assocd. with the differentiation of GOTO cells but that other events may also participate in this process.

L16 ANSWER 8 OF 11 BIOSIS COPYRIGHT 2000 BIOSIS

1993:165279 Document No.: PREV199395086329. Disturbing GTP-binding protein function through microinjection into the visual cell of Limulus. Stieve, Hennig (1); Niemeyer, Barbara; Aktories, Klaus; Hamm, Heidi E.. (1) Institut fuer Biologie II, RWTH Aachen, Kopernikusstrasse 6, D-W-5100 Aachen, Bundesrepublik Deutschland. Zietschrift fuer Naturforschung Section C Journal of Biosciences, (1992) Vol. 47, No. 11-12, pp. 915-921. Language: English.

AB We have tested the action of three agents microinjected into the ventral **nerve** photoreceptor of Limulus of the electrical response to dim light. 1. A monoclonal antibody (mAb 4A) against the G-alpha subunit of frog transducin reduces the size of the receptor current to 60%,

suggesting an interaction with G-alpha in the Limulus photoreceptor. 2. Injection of Clostridium botulinum ADP-ribosyltransferase **C3** reduces the size to 46%; latency is not affected. The results imply that small GTP-binding proteins play a functional role in photoreception of invertebrates. 3. Injection of GDP-beta-S reduces dose-dependently the size of the receptor current to 15% and prolongs that latency to 200%, presumably by reducing number and rate of G-protein activations..

L16 ANSWER 9 OF 11 MEDLINE DUPLICATE 4
91180965 Document Number: 91180965. ADP-ribosylation of cerebrocortical synaptosomal proteins by cholera, pertussis and botulinum toxins. Ashton A
C; Edwards K; Dolly J O. (Department of Biochemistry, Imperial College of Science, Technology and Medicine, London, England, U.K.) TOXICON, (1990) 28 (8) 963-73. Journal code: VWT. ISSN: 0041-0101. Pub. country: ENGLAND:
United Kingdom. Language: English.

AB Certain microbial toxins ADP-ribosylate G proteins that may be related to those postulated to participate in secretion, whilst botulinum neurotoxins, produced by Clostridium botulinum, block Ca2(+)-dependent neurotransmitter release. Thus, botulinum, pertussis and cholera toxins were examined for **ADP-ribosyl transferase** activity using isolated **nerve** terminals. Although type D botulinum, cholera and pertussis toxins exhibited such enzymic activity, this was not detectable with types A or B botulinum neurotoxins or their individual chains, in any synaptosomal fraction. Botulinum type D and pertussis toxins ADP-ribosylated proteins with mol. wt approximately 24,000 and 42,000 respectively, whereas cholera toxin modified several proteins including a 51,000/47,000 mol. wt doublet. Pre-incubation of synaptosomes with type A, B or D toxins did not inhibit type D-induced labelling in the corresponding lysate. Similar pre-incubations with cholera or pertussis toxins reduced ADP-ribosylation of their substrates. Hence, under conditions in which these botulinum toxins were shown to block Ca2(+)-dependent transmitter release no ADP-ribosylated substrate was produced in the intact **nerve** terminals. Moreover, direct correlation was not found between the concentration dependencies of type D
toxin for protein modification and inhibition of [3H]noradrenaline release
from synaptosomes. These collective findings implicate **C3**, a non-neurotoxic contaminant of type D, in the enzymic action. The substrate
for type D toxin was found in the cytosolic fraction and to a lesser extent in synaptic membranes, the reverse of the situation for pertussis toxin. A combination of the membranes and cytosol was required for maximal
labelling of the 51,000/47,000 doublet by cholera toxin. Purified synaptic
vesicles contained proteins labelled by type D and pertussis toxins but lacked major cholera toxin substrates. Future research will determine the possible involvement of these toxin-susceptible vesicular proteins in transmitter release.

L16 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 5
1991:626620 Document No. 115:226620 ADP-ribosylation of the rho/rac gene products by botulinum ADP-ribosyltransferase: identity of the enzyme and effects on protein and cell functions. Narumiya, Shuh; Morii, Narito; Sekine, Akihiro; Kozaki, Shunji (Fac. Med., Kyoto Univ., Kyoto, 606, Japan). J. Physiol. (Paris), 84(4), 267-72 (English) 1990. CODEN: JOPHAN. ISSN: 0021-7948.

AB A review with 21 refs. Botulinum C1 toxin and **C3** exoenzyme were

purified from the culture filtrate of type C Clostridium botulinum strain 003-9, and specific antibodies were raised against each protein. Immunochem. anal. using these antibodies revealed the presence of minute amt. of a **C3**-like mol. in the C1 toxin prepn. which tightly bound to the toxin component(s). This enzyme complex was sepd. from the major neurotoxin. Thus, the ADP-ribosyltransferases in C1 and D toxins and **C3** exoenzyme appear to arise from the same origin, and should be called together botulinum **C3** enzyme. Botulinum **C3** enzyme ADP-ribosylated the rho and rac gene products, a family of small-mol.-wt. GTP-binding proteins homologous to ras p21s. This ADP-ribosylation occurred at Asn-41 of the rho products which was located in their putative effector domain, suggesting that it interferes with the interaction of these GTP-binding proteins with their effector mols. When incubated with PC-12 cells, the enzyme inhibited cell growth and induced **neurites** and acetylcholinesterase. Several lines of evidence suggested that the ADP-ribosylation of the rho/rac proteins is responsible for these changes.

L16 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 6
1990:200494 Document No.: BA89:107165. ADP-RIBOSYLATION OF THE RHO-RAC PROTEINS INDUCES GROWTH INHIBITION **NEURITE** OUTGROWTH AND ACETYLCHOLINE ESTERASE IN CULTURED PC-12 CELLS. NISHIKI T; NARUMIYA S; MORII N; YAMAMOTO M; FUJIWARA M; KAMATA Y; SAKAGUCHI G; KOZAKI S. DEP. PHARMACOL., KYOTO UNIV. FAC. MED., YOSHIDA, SAKYO-KU, KYOTO 606, JPN.. BIOCHEM BIOPHYS RES COMMUN, (1990) 167 (1), 265-272. CODEN: BBRCA9. ISSN: 0006-291X. Language: English.

AB Botulinum ADP-ribosyltransferase **C3** (**C3** exoenzyme) was purified to homogeneity and added to cultured rat pheochromocytoma PC-12 cells. Incubation with this exoenzyme caused inhibition of cell growth and induced **neurites** as well as acetylcholine esterase in these cells. These changes were dependent on the amount of the enzyme added to the culture, which correlated with the in situ ADP-ribosylation of the rho/rac proteins in the cells. Preincubation with a specific anti-**C3** exoenzyme monoclonal antibody inhibited both the **ADP -ribosyl-transferase** activity and the **neurite** -inducing activity of the enzyme preparation. These results suggest that **C3** exoenzyme affected the cellular function of the rho/rac proteins by ADP-ribosylation to induce these changes in the cells.

'IN' IS NOT A VALID FIELD CODE
L17 21 FILE MEDLINE
L18 24 FILE CAPLUS
L19 53 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L20 17 FILE EMBASE
L21 4 FILE WPIDS

TOTAL FOR ALL FILES
L22 119 MCKERRACHER L?/AU,IN

'IN' IS NOT A VALID FIELD CODE
L23 450 FILE MEDLINE
L24 467 FILE CAPLUS
L25 621 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L26 426 FILE EMBASE

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L27         160 FILE WPIDS

TOTAL FOR ALL FILES
L28        2124 LEHMANN M?/AU,IN


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L29         926 FILE MEDLINE
L30         376 FILE CAPLUS
L31         840 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L32         585 FILE EMBASE
L33          61 FILE WPIDS

TOTAL FOR ALL FILES
L34        2788 FOURNIER A?/AU,IN

=> s l22 and l28 and l34

L35           1 FILE MEDLINE
L36           1 FILE CAPLUS
L37           3 FILE BIOSIS
L38           1 FILE EMBASE
L39           0 FILE WPIDS

TOTAL FOR ALL FILES
L40           6 L22 AND L28 AND L34

=> dup rem l40

PROCESSING COMPLETED FOR L40
L41           3 DUP REM L40 (3 DUPLICATES REMOVED)

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L41  ANSWER 1 OF 3  MEDLINE                                  DUPLICATE 1
1999389883  Document Number: 99389883.  Inactivation of Rho signaling pathway
     promotes CNS axon regeneration. Lehmann M; Fournier A;
     Selles-Navarro I; Dergham P; Sebok A; Leclerc N; Tigyi G; McKerracher
     L. (Departement de Pathologie et Biologie Cellulaire, Universite de
     Montreal, Succursale Centreville, Montreal, Quebec H3C 3J7, Canada. )
     JOURNAL OF NEUROSCIENCE, (1999 Sep 1) 19 (17) 7537-47.  Journal code:
JDF.
     ISSN: 0270-6474. Pub. country: United States. Language: English.
AB   Regeneration in the CNS is blocked by many different growth inhibitory
     proteins. To foster regeneration, we have investigated a strategy to
block
     the neuronal response to growth inhibitory signals. Here, we report that
     injured axons regrow directly on complex inhibitory substrates when Rho
     GTPase is inactivated. Treatment of PC12 cells with C3 enzyme to
     inactivate Rho and transfection with dominant negative Rho allowed
neurite
     growth on inhibitory substrates. Primary retinal neurons treated with C3
     extended neurites on myelin-associated glycoprotein and myelin
substrates.
     To explore regeneration in vivo, we crushed optic nerves of adult rat.
     After C3 treatment, numerous cut axons traversed the lesion to regrow in
     the distal white matter of the optic nerve. These results indicate that
     targeting signaling mechanisms converging to Rho stimulates axon
     regeneration on inhibitory CNS substrates.
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8 ANSWER 25 OF 30 MEDLINE
AN 91374122 MEDLINE
DN 91374122 PubMed ID: 1910076
TI Mono-**ADP-ribosylation** in brain: purification and characterization of **ADP-ribosyltransferases** affecting actin from rat brain.
AU Matsuyama S; Tsuyama S
CS Department of Veterinary Science, University of Osaka Prefecture, Japan.
SO JOURNAL OF NEUROCHEMISTRY, (1991 Oct) 57 (4) 1380-7.
Journal code: 2985190R. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199110
ED Entered STN: 19911108
Last Updated on STN: 20021218
Entered Medline: 19911021
AB Four **ADP-ribosyltransferases** that acted on non-muscle actin were purified more than 3,000-fold from rat brain extract. The molecular weights of these brain **ADP-ribosyltransferases** were 66,000 as estimated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and gel filtration on TSK gel G3000SW. The Km values for NAD were approximately 20 microM. These enzymes were not inhibited by thymidine or nicotinamide, but were inhibited by ADP and ADP-ribose. Two soluble **ADP-ribosylation** factors purified from rat brain had different effects on the four **ADP-ribosyltransferases** during the **ADP-ribosylation** of non-muscle actin. These **ADP-ribosyltransferases** modified not only actin but also the stimulatory guanine nucleotide-binding protein of adenylate cyclase, Gs, and another guanine nucleotide-binding protein in brain, Go. These findings suggest that the four brain **ADP-ribosyltransferases** are concerned with nerve functions in the **central nervous** system.

L3 ANSWER 32 OF 37 MEDLINE
AN 97442351 MEDLINE
DN 97442351 PubMed ID: 9298900
TI Role of a new Rho family member in cell migration and axon guidance in C. elegans.
AU Zipkin I D; Kindt R M; Kenyon C J
CS Department of Biochemistry and Biophysics, University of California, San Francisco 94143-0554, USA.
NC 5F32GM17924-02 (NIGMS)
5R01GM37053 (NIGMS)
SO CELL, (1997 Sep 5) 90 (5) 883-94.
Journal code: 0413066. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-U82288
EM 199710
ED Entered STN: 19971024
Last Updated on STN: 20000303
Entered Medline: 19971016
AB Rho family GTPases are thought to regulate actin-dependent processes, but their functions in vivo are still poorly understood. We have investigated the **function** of a new, widely expressed **Rho** family member in C. elegans by analyzing mutations in the endogenous gene. Activated and null alleles all **inhibit** cell migration, demonstrating that this protein is required for cell migration in vivo. Only a small subset of the migrations **inhibited** by activating mutations are **inhibited** by null mutations, suggesting that considerable functional redundancy exists within this system. Our findings support this conclusion and show that mig-2 functions redundantly with another pathway to regulate nuclear migration. Surprisingly, activated alleles also cause misguided axon growth, suggesting that Rho family GTPases may couple guidance cues to process outgrowth.

L3 ANSWER 33 OF 37 MEDLINE
AN 97246707 MEDLINE
DN 97246707 PubMed ID: 9092945
TI **Rac** is required for growth cone **function** but not **neurite** assembly.
AU Lamoureux P; Altun-Gultekin Z F; Lin C; Wagner J A; Heidemann S R
CS Department of Physiology, Michigan State University, East Lansing 48824, USA.
NC EY06454 (NEI)
GM36894 (NIGMS)
NS31728 (NINDS)
SO JOURNAL OF CELL SCIENCE, (1997 Mar) 110 (Pt 5) 635-41.
Journal code: 0052457. ISSN: 0021-9533.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199706
ED Entered STN: 19970620
Last Updated on STN: 20000303
Entered Medline: 19970606
AB Recent work has suggested that rac1 and other members of the rho family of small GTP-binding proteins play an important role in the formation of **neural** processes. We have explored the mechanism of this effect by comparing the spontaneous, growth cone-mediated growth and experimental tension-induced growth of axons in normal PC12 cells and in mutant cells expressing a dominant negative form of rac. PC12 that have been primed by exposure to NGF, but not naive PC12 cells, initiate a microtubule-rich process de novo in response to tension applied to cell body. As in chick sensory **neurons**, **neurite** elongation rate is proportional to applied tension above a threshold. Addition of cyclic AMP, which has been shown to rapidly augment NGF-induced **neurite** outgrowth in PC12, causes a rapid increase in the rate of **neurite** elongation at a given tension level. Expression of a dominant negative form of rac1 **inhibits** spontaneous, growth cone-mediated **neurite** elongation in response to NGF, but does not substantially affect tension-induced **neurite** elongation. That is, rac-deficient cells show a normal linear relationship between applied tension and elongation rate and the elongations contain a normal density of axial microtubules by immunofluorescent assay. Thus, rac1 is apparently required for the mechanisms that normally generate tension in an elongating **neurite**, but if this tension is provided from an outside source, then axonal elongation can proceed normally in rac1-deficient cells. We conclude that rac1 is required for the adhesive and motile function of growth cones rather than the assembly of **neurites** per se.

L8 ANSWER 3 OF 4 MEDLINE
AN 1999087521 MEDLINE
DN 99087521 PubMed ID: 9872486
TI Raloxifene induces neurite outgrowth in estrogen receptor positive PC12 cells.
AU Nilsen J; Mor G; Naftolin F
CS Department of Obstetrics and Gynecology and Center for Reproductive Biology, Yale University School of Medicine, New Haven, Connecticut 06520-8063, USA.
SO MENOPAUSE, (1998 Winter) 5 (4) 211-6.
Journal code: 9433353. ISSN: 1072-3714.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
ED Entered STN: 19990316
Last Updated on STN: 20000303
Entered Medline: 19990303
AB OBJECTIVE: It is well established that gonadal steroids have direct in **vivo** and in **vitro** effects on neurons. To further study these effects, we used rat **PC 12** cells to examine the effects of estrogen receptor (ER) ligands on neuronal morphology. DESIGN: **PC 12** cells constitutively express ER beta, but only strongly express ER alpha after long-term priming with nerve growth factor (**NGF**). We therefore primed PC12 cells with **NGF** for 14 days before testing them for estradiol (10(-9)M)- and/or raloxifene (10(-7) M)-induced neurite growth. Neurite growth was assessed by quantitative light microscopy. As control, ER status of the PC12 cells was assessed by reverse transcription-polymerase chain reaction (RT-PCR). RESULTS: In this study, both estradiol and raloxifene induced the outgrowth of neurites in **NGF**-treated **PC 12** cells ($p < 0.05$). The combination of estradiol- and raloxifene-induced neurite growth was statistically greater than the effects of either agent alone. RT-PCR confirms that **NGF**-treated **PC 12** cells express both ERalpha and ERbeta. CONCLUSIONS: This report is the first on the neurotrophic effect of raloxifene. At 10(-7) M, raloxifene's effect equaled that of estradiol; moreover, raloxifene did not block the neurite growth of simultaneously estradiol-treated **PC 12** cells, despite its functional antiestrogenic effects in **vivo**. We conclude that raloxifene is estrogen agonistic in this animal model and therefore studies are warranted to delineate the relationship between steroidal estrogen and raloxifene.

L8 ANSWER 4 OF 4 MEDLINE
AN 97216450 MEDLINE
DN 97216450 PubMed ID: 9062679
TI Influence of nefiracetam on **NGF**-induced neuritogenesis and neural cell adhesion molecule polysialic acid expression: in **vivo** and in **vitro** comparisons.
AU Odumeru O; Murphy K J; O'Connell A W; Regan C M; Shiotani T
CS Department of Pharmacology, University College Dublin, Ireland.
SO BEHAVIOURAL BRAIN RESEARCH, (1997 Feb) 83 (1-2) 173-8.
Journal code: 8004872. ISSN: 0166-4328.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199707
ED Entered STN: 19970721
Last Updated on STN: 19970721

Entered Medline: 19970709

AB Previously, the ability of co-administered nefiracetam to reverse scopolamine-induced learning deficits has been attributed to the preservation of a transient increase in neural cell adhesion molecule (NCAM) polysialylation state during a late phase of memory consolidation (Doyle et al., J. Neurosci. Res., 31 (1992) 513-523). Using the **PC-12** pheochromocytoma cell model, we now demonstrate nefiracetam pre-exposure to significantly enhance nerve growth factor-induced neuritogenesis and NCAM polysialylation, but not prevalence, in a dose-dependent manner with maximal effects being observed at the lowest dose (0.1 microM) examined. As the memory-associated increase in NCAM polysialylation in **vivo** is associated with a defined group of neurons at the dentate hilar/granule cell layer border (Regan and Fox, Neurochem. Res., 20 (1995) 521-526), the effect of chronic nefiracetam exposure in **vivo** was evaluated. Once-daily, intraperitoneal administration of either 3 or 9 mg/kg nefiracetam to adult male Wistar rats for 40 days significantly increased the number of hippocampal dentate polysialylated neurons only at the highest dose evaluated, suggesting it to prevent their age-dependent decline. These results are consistent with nefiracetam facilitating early induction events of long-term memory consolidation processes involving NCAM polysialylation state.

=>

L3 ANSWER 36 OF 37 MEDLINE
AN 90179760 MEDLINE
DN 90179760 PubMed ID: 2106882
TI **ADP-ribosylation** of the rho/rac proteins induces growth **inhibition, neurite** outgrowth and acetylcholine esterase in cultured PC-12 cells.
AU Nishiki T; Narumiya S; Morii N; Yamamoto M; Fujiwara M; Kamata Y; Sakaguchi G; Kozaki S
CS Department of Pharmacology, Kyoto University Faculty of Medicine, Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1990 Feb 28) 167 (1) 265-72.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199004
ED Entered STN: 19900601
Last Updated on STN: 20000303
Entered Medline: 19900402
AB Botulinum **ADP-ribosyltransferase** C3 (C3 exoenzyme) was purified to homogeneity and added to cultured rat pheochromocytoma PC-12 cells. Incubation with this exoenzyme caused **inhibition** of cell growth and induced **neurites** as well as acetylcholine esterase in these cells. These changes were dependent on the amount of the enzyme added to the culture, which correlated with the in situ **ADP-ribosylation** of the rho/rac proteins in the cells. Preincubation with a specific anti-C3 exoenzyme monoclonal antibody **inhibited** both the **ADP-ribosyltransferase** activity and the **neurite**-inducing activity of the enzyme preparation. These results suggest that C3 exoenzyme affected the cellular **function** of the **rho/rac** proteins by **ADP-ribosylation** to induce these changes in the cells.

102 inherency?

L6 ANSWER 2 OF 3 MEDLINE
AN 94338461 MEDLINE
DN 94338461 PubMed ID: 8060425
TI Magnetic resonance spectroscopy in Niemann-Pick disease type C: correlation with diagnosis and clinical response to cholestyramine and **lovastatin**.
AU Sylvain M; Arnold D L; Scriver C R; Schreiber R; Shevell M I
CS Department of Neurology/NeuroSurgery, McGill University, Montreal, Canada.
SO PEDIATRIC NEUROLOGY, **(1994 May)** 10 (3) 228-32.
Journal code: 8508183. ISSN: 0887-8994.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199409
ED Entered STN: 19941005
Last Updated on STN: 20020125
Entered Medline: 19940920
AB Niemann-Pick type C is an autosomal-recessive, **neurovisceral** storage disorder that results from defective cholesterol esterification. Cholesterol-lowering agents have been demonstrated to decrease hepatic lipids in Niemann-Pick type C patients. The objective was to determine the effects of cholesterol-lowering agents on **neurologic** features and to develop a noninvasive method of monitoring clinical response. A 9-month-old boy with progressive hepatosplenomegaly and **neurodevelopmental** delay was studied. Water-suppressed proton magnetic resonance spectra from a supraventricular volume of central white and gray matter revealed an abnormal lipid signal. The patient was treated with cholesterol-lowering agents (i.e., cholestyramine, **lovastatin**). Repeat standardized **neurodevelopmental** assessments (Peabody and Griffith scales) at 13 and 19 months were normal and magnetic resonance spectra no longer detected the previously observed lipid resonance. Early treatment of Niemann-Pick type C patients with cholesterol-lowering agents appeared to have short-term beneficial effects. Magnetic resonance spectra provided a noninvasive means of monitoring CNS response.

L6 ANSWER 3 OF 3 MEDLINE
AN 93141022 MEDLINE
DN 93141022 PubMed ID: 8423912
TI The effect of cholesterol-lowering agents on hepatic and plasma cholesterol in Niemann-Pick disease type C.
AU Patterson M C; Di Bisceglie A M; Higgins J J; Abel R B; Schiffmann R; Parker C C; Argoff C E; Grewal R P; Yu K; Pentchev P G; +
CS Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892.
SO NEUROLOGY, **(1993 Jan)** 43 (1) 61-4.
Journal code: 0401060. ISSN: 0028-3878.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199302
ED Entered STN: 19930312
Last Updated on STN: 20000303
Entered Medline: 19930223
AB Niemann-Pick disease type C (NP-C) is a **neurovisceral** lipidosis characterized by defective intracellular trafficking of cholesterol and lysosomal accumulation of unesterified cholesterol, believed to be an

offending metabolite. We studied the effect of cholesterol-lowering agents on hepatic and plasma cholesterol levels in NP-C by randomly assigning 25 patients with NP-C to one of five treatment regimens containing different combinations of cholestyramine, **lovastatin,** nicotinic acid, or dimethyl sulfoxide (DMSO). Unesterified cholesterol content was measured in liver biopsies before and after 4 months' treatment. All drug regimens except DMSO alone reduced hepatic and plasma cholesterol levels. Toxicity was limited and did not prevent any patient from completing the study. The combination of cholestyramine, **lovastatin,** and nicotinic acid lowered cholesterol levels in liver and blood with minimal side effects. A controlled clinical study will be necessary to determine if this regimen influences the rate of **neurologic** progression.

L3 ANSWER 21 OF 23 MEDLINE
AN 83257639 MEDLINE
DN 83257639 PubMed ID: 6409178
TI Model clonal system for study of neuronal cell injury.
AU Perez-Polo J R; Tiffany-Castiglioni E; Werrbach-Perez K
NC NS00213 (NINDS)
NS14034 (NINDS)
SO BIRTH DEFECTS ORIGINAL ARTICLE SERIES, **(1983)** 19 (4) 201-20.
Journal code: 0003403. ISSN: 0547-6844.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198309
ED Entered STN: 19900319
Last Updated on STN: 19980206
Entered Medline: 19830923

PC-12 model system

L7 ANSWER 46 OF 48 MEDLINE
AN 82222341 MEDLINE
DN 82222341 PubMed ID: 7088968
TI **NGF** effects on human **neuroblastoma** lines: a **model** system.
AU Perez-Polo J R; Reynolds C P; Tiffany-Castiglioni E; Ziegler M; Schulze I; Werrback-Perez K
SO PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, **(1982)** 79 285-99.
Journal code: 7605701. ISSN: 0361-7742.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198208
ED Entered STN: 19900317
Last Updated on STN: 19900317
Entered Medline: 19820826

L7 ANSWER 47 OF 48 MEDLINE
AN 81122711 MEDLINE
DN 81122711 PubMed ID: 6162093
TI Regulation of presynaptic cellular function. Biochemical studies using clonal neuronal cells.
AU McGee R Jr
SO MOLECULAR AND CELLULAR BIOCHEMISTRY, **(1980 Dec 16)** 33 (3) 121-33. Ref: 62
Journal code: 0364456. ISSN: 0300-8177.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 198104
ED Entered STN: 19900316
Last Updated on STN: 19980206
Entered Medline: 19810421
AB Experiments from several different laboratories are reviewed in which clonal neuronal cell lines are being used to study neuronal cellular functions. Primary emphasis is placed on two cell lines, the **neuroblastoma** X glioma hybrid clone NG108-15 and the pheochromocytoma clone PC12. These particular cell lines are useful because they display many of the properties normally associated with differentiated neurons. The properties which have been studied include: the regulation of adenylate cyclase and the receptors which activate or inhibit its activity, regulation of the cholinergic properties of NG 108-15 and both adrenergic and cholinergic properties of PC12, the response of PC12 to **nerve growth factor**, and the regulation of synaptogenesis between NG 108-15 cells and cultured muscle. The goal of the **review** is to not only summarize the information obtained with these two cell lines but also to emphasize the types of research in which clonal cell lines may be most useful in the future.

L7 ANSWER 48 OF 48 MEDLINE
AN 80047615 MEDLINE
DN 80047615 PubMed ID: 499664
TI A human clonal cell line **model** of differentiating neurons.
AU Perez-Polo J R; Werbach-Perez K; Tiffany-Castiglioni E
SO DEVELOPMENTAL BIOLOGY, **(1979 Aug)** 71 (2) 341-55.
Journal code: 0372762. ISSN: 0012-1606.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198001
ED Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19800119

L8 ANSWER 1 OF 8 MEDLINE
AN 1998067228 MEDLINE
DN 98067228 PubMed ID: 9404724
TI Responses of cortical noradrenergic and somatostinergic fibres and terminals to adjacent **strokes** and subsequent treatment with **NGF** and/or the ganglioside GM1.
AU Tajrine D; Garofalo L; Cuello A C; Ribeiro-da-Silva A
CS Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada.
SO JOURNAL OF NEUROSCIENCE RESEARCH, **(1997 Nov 15)** 50 (4) 627-42.
Journal code: 7600111. ISSN: 0360-4012.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980129
AB The occurrence of sprouting by fibre systems in the neocortex following lesion is still a controversial issue. In previous studies, we showed a nerve growth factor (**NGF**)-induced sprouting and hypertrophy of presynaptic terminals in the cholinergic fibres of the rat neocortex following **stroke**-type lesions, effects that were potentiated by the monosialoganglioside GM1. The present study investigated whether exogenous **NGF** and/or GM1 treatment could also affect the noradrenergic and somatostinergic systems in the neocortex. Immediately following unilateral vascular decortication, adult rats received, via minipump, a 7-day infusion of vehicle, **NGF** (12 microg/day) and/or GM1 (1.5 mg/day) into the cerebroventricular space. Thirty days postlesion, the animals were perfused with histological fixatives, the brains were removed, and relevant sections were processed for dopamine beta-hydroxylase and somatostatin immunocytochemistry at the light and electron microscopic levels. A Quantimet 920 image analysis system was used for the quantification of fibre length and size of presynaptic boutons. The lesion caused a reduction in the dopamine beta-hydroxylase-immunoreactive fibre length, which was not attenuated by either **NGF** or GM1 treatment or both. The somatostatin-immunoreactive network, in contrast, was unaffected by the lesion, and there was no sprouting of somatostatin fibres following trophic factor therapy. We also found no significant differences in the size and number of synapses of both the dopamine beta-hydroxylase-immunoreactive and somatostatin-immunoreactive boutons following lesion and drug treatments. These results indicate that **NGF** and/or GM1 therapies do not cause regrowth in the noradrenergic and somatostatinergic cortical fibre networks or their presynaptic elements following a cortical devascularizing lesion.

L1 ANSWER 3 OF 3 MEDLINE
AN 94152334 MEDLINE
DN 94152334 PubMed ID: 8109297
TI Reparative strategies in the brain: treatment strategies based on trophic factors and cell transfer techniques.
AU Olson L
CS Department of Histology and Neurobiology, Karolinska Institutet, Sweden.
NC AG04418 (NIA)
NS 09199 (NINDS)
SO ACTA NEUROCHIRURGICA. SUPPLEMENTUM, (1993) 58 3-7. Ref: 23
Journal code: 0140560. ISSN: 0065-1419.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199403
ED Entered STN: 19940330
Last Updated on STN: 20000303
Entered Medline: 19940324
AB Three reparative strategies based on transfer of genes, molecules, or cells to the central nervous system are reviewed. When neurons are already lost, they can sometimes be replaced by transfer to the target area of neurons or other cells compensating for the lost functions. This technique is undergoing clinical trials in Parkinson's disease. Before neurons have died, it may be possible to prevent "stressed" neurons from dying, and stimulate nerve terminal ramifications from remaining neurons using treatment with neurotrophic factors. Such approaches, with an emphasis on the **NGF** family of neurotrophins and their receptors, are reviewed. Finally, advances of molecular biology techniques suggest that it should be possible to transfer genes directly into non-dividing cells of the central nervous system. The three different approaches all aim at long-lasting counteractive and reparative measures in the central nervous system. It is predicted that they have general applicability, and may become important not only in neurodegenerative diseases, but also in other common afflictions of the nervous system such as ischaemia, **stroke** and injury.

L13 ANSWER 9 OF 22 MEDLINE
AN 97383275 MEDLINE
DN 97383275
TI Rac1 mediates collapsin-1-induced growth cone collapse.
AU Jin Z; Strittmatter S M
CS Department of Neurology, Yale University School of Medicine, New Haven, Connecticut 06520, USA.
SO JOURNAL OF NEUROSCIENCE, (1997 Aug 15) 17 (16) 6256-63.
Journal code: JDF. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199710
AB Collapsin-1 or semaphorin III(D) inhibits **axonal** outgrowth by collapsing the lamellipodial and filopodial structures of the **neuronal** growth cones. Because growth cone collapse is associated with actin depolymerization, we considered whether small GTP-binding proteins of the rho subfamily might participate in collapsin-1 signal transduction. Recombinant rho, rac1, and cdc42 proteins were triturated into embryonic chick (DRG) **neurons**. Constitutively active rac1 increases the proportion of collapsed growth cones, and dominant negative rac1 inhibits collapsin-1-induced collapse of growth cones and collapsin-1
inhibition of neurite outgrowth. DRG **neurons** treated with dominant negative rac1 remain sensitive to myelin-induced growth cone collapse. Similar mutants of cdc42 do not alter growth cone structure, neurite elongation, or collapsin-1 sensitivity. Whereas the addition of activated rho has no effect, the inhibition of rho with Clostridium **botulinum C3 transferase** stimulates the outgrowth of DRG neurites. C3 transferase-treated growth cones exhibit little or no lamellipodial spreading and are minimally responsive to collapsin-1 and myelin. These data demonstrate a prominent role for rho and rac1 in modulating growth cone motility and indicate that rac1 may mediate collapsin-1 action.

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8-15-97 pd: not perfected.
10-31-97 pd
8-15-98 102(b) date

11-2-98 fd.

P14 3-9
28 16-26
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L6 ANSWER 5 OF 5 MEDLINE
AN 93176163 MEDLINE
DN 93176163 PubMed ID: 8439316
TI Evidence for an indirect effect of **nerve growth** factor (NGF) on the ADP-ribosylation of a 22 kDa rho-like protein in PC12 cells.
AU Takahashi H; Guroff G
CS Section on Growth Factors, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1993 Feb 15) 190 (3) 1156-62.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
ED Entered STN: 19930402
Last Updated on STN: 20000303
Entered Medline: 19930323
AB EDIN catalyzes the ADP-ribosylation of a 22 kDa protein, probably related to rho, in permeabilized PC12 cells in a time- and dose-dependent manner. Pre-treatment of the cells with **nerve growth** factor inhibits this EDIN-catalyzed ADP-ribosylation, both in vitro and in **vivo**. This inhibition is largely prevented by the addition of K-252a. **Nerve growth** factor itself causes neither ADP-ribosylation nor phosphorylation of this 22 kDa protein. These results suggest that the ADP-ribosylation of the **rho** protein is **inhibited**, albeit indirectly, by **nerve growth** factor treatment.

L9 ANSWER 11 OF 11 MEDLINE
AN 87052863 MEDLINE
DN 87052863 PubMed ID: 3536312
TI The role of growth factors in neuronal development and plasticity.
AU Crutcher K A
NC NS 17131 (NINDS)
SO CRC CRITICAL REVIEWS IN CLINICAL NEUROBIOLOGY, (1986) 2 (3) 297-333. Ref: 343
Journal code: 8506657. ISSN: 0742-941X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Priority Journals
EM 198612
ED Entered STN: 19900302
Last Updated on STN: 19970203
Entered Medline: 19861223
AB The role of growth factors in the development of the nervous system, as well as in injury-induced plasticity, is of great interest. A neuronal growth factor is any substance that influences the growth of neurons, but two general classes of factors exist: diffusible substances and substrate-bound factors. Growth factors may affect neuronal survival as well as the extent and rate of neurite **outgrowth** in vitro. Although progress is slowly being made in the identification and characterization of putative growth factors, nerve growth factor (**NGF**) is the only identified molecule that clearly influences neuronal growth in **vivo**. Furthermore, although there are many examples of neuronal plasticity following injury, the role of growth factors in such rearrangements remains to be established. However, one model of collateral sprouting of axons from the peripheral nervous system (PNS) into the central nervous system (**CNS**) appears to involve the action of a growth factor with properties similar to **NGF**. The identification of specific molecules that affect neuronal growth should lead to an understanding of the etiology of degenerative neurological diseases such as Alzheimer's disease and, hopefully, to rational therapeutic approaches.

L6 ANSWER 1 OF 6 Elsevier BIOBASE COPYRIGHT 2000 Elsevier Science B.V.
DUPLICATE
AB Rat **optic nerves** were subjected to **crush**
injury to study the local tissue reactions leading to wound healing and
tissue **repair**. We used antibodies against glial fibrillary
acidic protein (GFAP), vimentin, the S100 protein (S100P), lysozyme, and
ED1 as markers for. . .

L6 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2
AB Gangliosides have been shown to be capable of protecting nerve tissue
from
mechanical and biochemical insults and promoting their **repair**.
The present study provides morphologic evidence that
monosialogangliosides
attenuate the degenerative process at the distal stump of the rat
optic nerve after **crush** injury. Injured rat
optic nerves were treated for 7 days after injury with daily
intraperitoneal injections of monosialogangliosides (30 mg/kg/day),. .
.

L6 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 3
AB. . . developed model of the 'graded optic nerve crush' is compared with
other models of lesioning. It is concluded that the **optic**
nerve crush model is a valuable tool when studying brain
repair mechanisms. First results show that functional recovery
depends on the initial preservation of a sufficiently large population of
ganglion cells. . .

L6 ANSWER 4 OF 6 MEDLINE
AB . . . be most similar to neuropeptide-Y. Radioimmunoassay and
immunocytochemical staining of retinas in which the efferent fiber
peptide
was depleted by **optic nerve crush** confirm in
large part the observation that the two peptide systems are distinct.
However, there is some **cross**-recognition of the FMRF amide-like
tissue antigen by pancreatic polypeptide antibodies. Double-label studies
with antisera to tyrosine hydroxylase and neuropeptide-Y indicate. . .

L6 ANSWER 5 OF 6 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 4
AB . . . distribution of laminin in the goldfish visual system.
Immunoperoxidase staining for laminin showed a characteristic scalloped
pattern of staining in **cross**-sections of **optic**
nerve bundles. Following **optic nerve**
crush, the reaction of product became much more diffuse and
intense, especially distal to the crush site. When the retinal ganglion.
. .

L6 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 5
AB. . . tecta, 9 days to 9 months postoperatively, by means of
immunohistochemical methods. Peptide-like immunoreactivity was observed
in
axons within the **optic nerve** stump retinal to the
crush, as in previous studies (Kuljis and Karten, 83b, Kuljis et
al., 84). Peptide-containing retinofugal axons began **traversing**
the lesion site between 10 and 20 days postoperatively, in progressively
increasing numbers. Ten to 20 days following **crush** of the
optic nerve SP-, LENK-, and CCK8-containing axons could
be found in the cerebral stump of the optic nerve and in the optic. . .

=> d bib ab 1-3, 6

L6 ANSWER 1 OF 6 Elsevier BIOBASE COPYRIGHT 2000 Elsevier Science B.V. DUPLICATE
AN 1996125845 Elsevier BIOBASE
TI Cellular reactions at the lesion site after crushing of the rat optic nerve
AU Frank M.; Wolburg H.
CS M. Frank, Institut fur Hirnforschung, Universitat Zurich, August-Forel-Strasse 1, CH-8029 Zurich, Switzerland.
SO GLIA, (1996), 16/3 (227-240)
CODEN: GLIAEJ ISSN: 0894-1491
DT Journal; Article
CY United States
LA English
SL English
AB Rat **optic nerves** were subjected to **crush** injury to study the local tissue reactions leading to wound healing and tissue **repair**. We used antibodies against glial fibrillary acidic protein (GFAP), vimentin, the S100 protein (S100P), lysozyme, and ED1 as markers for astroglial cells and microglia/macrophages at the light and electron microscopic level during the 3 weeks following the crush. The crush injury produced a vast area of tissue damage including the disruption of the blood-brain barrier (BBB). In the first days after crushing, astrocytes were absent from the lesion site. S100P-positive astrocytes reappeared in the lesion center as early as 6 days after crushing. These astrocytes reestablished former topological structures such as perivascular and subpial glia limitans. At the edges of the lesion site reactive astrocytes enclosed and embedded axonal and myelin debris. Preceding the astroglial repopulation, a massive infiltration of microglia/macrophages (phagocytes) into the lesion center took place. ED1- positive/lysozyme-positive cells of round shape were seen in the lesion center at 2 days after crushing, and their number peaked around I week after crushing. They efficiently cleared the debris from the lesion site and mostly disappeared after 3 weeks. With immuno-electron microscopy we found the ED1 antigen related to the membranes of phagosomes. The microglia/macrophages observed in the nerve segments distal of the lesion (Wallerian degeneration site) were different from those in the lesion center: 1) they appeared later, about 6 days after crushing; 2) they were ED1 positive, but lysozyme negative and showed a branched morphology; and 3) they persisted in the distal nerve segment but showed little phagocytosis. We suggest that these cells are mostly activated microglia.

L6 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 2
AN 1993:437160 BIOSIS
DN PREV199396091785
TI Gangliosides attenuate axonal loss after optic nerve injury.
AU Zalish, Miriam (1); Lavie, Vered; Duvdevani, Revital; Yoles, Eti; Schwartz, Michal
CS (1) Dep. Ophthalmol., Kaplan Hosp., 76100 Rehovot Israel
SO Retina, (1993) Vol. 13, No. 2, pp. 145-147.
ISSN: 0275-004X.
DT Article
LA English
AB Gangliosides have been shown to be capable of protecting nerve tissue from mechanical and biochemical insults and promoting their **repair**. The present study provides morphologic evidence that monosialogangliosides attenuate the degenerative process at the distal stump of the rat **optic nerve** after **crush** injury. Injured rat optic nerves were treated for 7 days after injury with daily intraperitoneal injections of monosialogangliosides (30 mg/kg/day), and

compared with untreated injured controls with respect to the number of viable axons 2 and 4 weeks after injury, as indicated by transmission electron microscopy. After 2 weeks, the mean number of viable axons in the treated optic nerves (n = 5) was slightly higher than in the controls (n = 5). Four weeks after injury, although the absolute number in both the experimental and the control groups had dropped, it was about seven-fold higher in the treated animals (1696 +- 1149, n = 7) than in the untreated animals (216 +- 65, n = 6); this difference was statistically significant.
These findings, which offer some insight as to how monosialogangliosides affect injured nerves, may have important implications for treatment in cases of optic nerve injury.

L6 ANSWER 3 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 3
AN 1993:588833 BIOSIS
DN PREV199497008203
TI Functional recovery and morphological changes after injury to the optic nerve.
AU Sabel, B. A. (1); Ashoff, A.
CS (1) Inst. Med. Psychol., Med. Sch. Magdeburg, Leipzigerstrase 44, D-39120 Magdeburg Germany
SO Neuropsychobiology, (1993) Vol. 28, No. 1-2, pp. 62-65.
ISSN: 0302-282X.
DT Article
LA English
AB Physiological and morphological parameters of optic nerve lesions followed by functional recovery are discussed in detail. To study functional and/or morphological recovery processes, a recently developed model of the 'graded optic nerve crush' is compared with other models of lesioning. It is concluded that the **optic nerve crush** model is a valuable tool when studying brain **repair** mechanisms. First results show that functional recovery depends on the initial preservation of a sufficiently large population of ganglion cells in the retina. It takes place despite the progressive loss of retinal ganglion cells during the recovery period.

L6 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 5
AN 1986:115441 BIOSIS
DN BA81:25857
TI REGENERATION OF PEPTIDE-CONTAINING RETINOFUGAL AXONS INTO THE OPTIC TECTUM WITH REAPPEARANCE OF A SUBSTANCE P-CONTAINING LAMINA.
AU KULJIS R O; KARTEN H J
CS SECTION NEUROANATOMY, YALE UNIV., 333 CEDAR ST., NEW HAVEN, CT 06510.
SO J COMP NEUROL, (1985) 240 (1), 1-15.
CODEN: JCNEAM. ISSN: 0021-9967.
FS BA; OLD
LA English
AB Twenty-five specimens of Rana pipiens were subjected to a unilateral crush of the optic nerve. Substance P (SP)-, leucine enkephalin (LENK)-, cholecystokinin octapeptide (CCK8)-, and bombesin (BOM)-like immunoreactivities were analyzed in the retinae, optic nerves, and optic tecta, 9 days to 9 months postoperatively, by means of immunohistochemical methods. Peptide-like immunoreactivity was observed in axons within the **optic nerve** stump retinal to the **crush**, as in previous studies (Kuljis and Karten, 83b, Kuljis et al., 84). Peptide-containing retinofugal axons began **traversing** the lesion site between 10 and 20 days postoperatively, in progressively increasing numbers. Ten to 20 days following **crush** of the **optic nerve** SP-, LENK-, and CCK8-containing axons could be found in the

cerebral stump of the optic nerve and in the optic chiasm, advancing to the side of the brain deafferented by the crush. The number of axons displaying peptide-like immunoreactivity within the optic nerve, retinal or cerebral to the crush, and within the optic chiasm gradually decreased after 2-3 months. The optic nerve contralateral to the procedure displayed only occasional isolated peptide-containing fibers, as in normal optic nerves. The retinae ipsilateral and contralateral to the crush exhibited no change in the normal pattern of peptide-like immunoreactivity, including the absence of demonstrable peptide-like immunoreactivity in the somata of retinal ganglion cells. The optic tectum deafferented by the procedure underwent modifications in the pattern of peptide-like immunoreactivity identical to those reported following unilateral eye enucleation (Kuljis and Karten, 82a, 83a). The patterns of LENK-, CCK8-, and BOM-like immunoreactivities in the tectum were identical to those following irreversible retinal deafferentation as long as 9 months postoperatively. SP-like immunoreactivity, however, was gradually restored in layer 11 of Ramon y Cajal ('46; layer D of Potter, 69) of the superficial (retinorecipient) neuropil 4-6 months postoperatively. The persistence of lamina-specific depletion patterns of LENK-, CCK8-, and BOM-like immunoreactivities in reafferented tecta represents a puzzling observation. The latter findings contrast sharply with the recovery of SP-like immunoreactivity, which occurs long after apparently complete restitution of the retinofugal projection, as shown by anatomical (Stelzner et al., 81), physiological (Maturana et al., 59), and behavioral (Sperry, 44) methods. The implications of these findings are discussed with particular reference to the possibility of lamina-specific reinnervation of the tectum by SP-containing retinofugal axons; the possible roles of peptides in the adjustment or modulation of retinofugal input processing in the tectum; the possibility of a differential capability for successful regeneration and/or specific reinnervation of the various populations of peptide-containing retinal ganglion cells; and the possibility of selective death of some of the peptide-containing retinal ganglion cell populations as a result of inability to regenerate or abortive regeneration.

TI **Inhibition** of lysophosphatidate- and thrombin-induced neurite retraction and **neuronal** cell rounding by ADP ribosylation of the small GTP-binding protein **Rho**.

AU Jalink K; van Corven E J; Hengeveld T; Morii N; Narumiya S; Moolenaar W H
CS Division of Cellular Biochemistry, The Netherlands Cancer Institute, Amsterdam.

SO JOURNAL OF CELL BIOLOGY, (1994 Aug) 126 (3) 801-10.
Journal code: HMV. ISSN: 0021-9525.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199411

AB Addition of the bioactive phospholipid lysophosphatidic acid (LPA) or a thrombin receptor-activating peptide (TRP) to serum-starved N1E-115 or NG108-15 neuronal cells causes rapid growth cone collapse, neurite retraction, and transient rounding of the cell body. These shape changes appear to be driven by receptor-mediated contraction of the cortical actomyosin system independent of classic second messengers. Treatment of the cells with Clostridium botulinum C3 exoenzyme, which ADP-ribosylates and thereby inactivates the Rho small GTP-binding protein, inhibits LPA- and TRP-induced force generation and subsequent shape changes. C3 also inhibits LPA-induced neurite retraction in PC12 cells. Biochemical analysis reveals that the ADP-ribosylated substrate is RhoA. Prolonged C3 treatment of cells maintained in 10% serum induces the phenotype of serum-starved cells, with initial cell flattening being followed by neurite outgrowth; such C3-differentiated cells fail to retract their neurites in response to agonists. We conclude that RhoA is essential for receptor-mediated force generation and ensuing neurite retraction in N1E-115 and PC12 cells, and that inactivation of RhoA by ADP-ribosylation abolishes actomyosin contractility and promotes neurite outgrowth.

DN 96347576
TI The GTPase-activating protein n-chimaerin cooperates with Rac1 and Cdc42Hs
to induce the formation of lamellipodia and filopodia.
AU Kozma R; Ahmed S; Best A; Lim L
CS Department of Neurochemistry, Institute of Neurology, London, United Kingdom.
SO MOLECULAR AND CELLULAR BIOLOGY, (1996 Sep) 16 (9) 5069-80.
Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199611
AB n-Chimaerin is a GTPase-activating protein (GAP) mainly for Rac1 and less so for Cdc42Hs in vitro. The GAP activity of n-chimaerin is regulated by phospholipids and phorbol esters. Microinjection of Rac1 and Cdc42Hs into mammalian cells induces formation of the actin-based structures lamellipodia and filopodia, respectively, with the former being prevented by coinjection of the chimaerin GAP domain. Strikingly, microinjection of the full-length n-chimaerin into fibroblasts and neuroblastoma cells induces the simultaneous formation of lamellipodia and filopodia. These structures undergo cycles of dissolution and formation, resembling natural morphological events occurring at the leading edge of fibroblasts and **neuronal** growth cones. The effects of n-chimaerin on formation of lamellipodia and filopodia were **inhibited** by dominant negative Rac1(T17N) and Cdc42Hs(T17N), respectively. n-Chimaerin's effects were also inhibited by coinjection with **Rho** GDP dissociation inhibitor or by treatment with phorbol ester. A mutant n-chimaerin with no GAP activity and impaired p21 binding was ineffective in inducing morphological changes, while a mutant lacking GAP activity alone was effective. Microinjected n-chimaerin colocalized in situ with F-actin. Taken together, these results suggest that n-chimaerin acts synergistically with Rac1 and Cdc42Hs to induce actin-based morphological changes and that this action involves Rac1 and Cdc42Hs binding but not GAP activity. Thus, GAPs may have morphological functions in addition to downregulation of GTPases.

TI Thrombin induces apoptosis in cultured neurons and astrocytes via a pathway requiring tyrosine kinase and RhoA activities.

AU Donovan F M; Pike C J; Cotman C W; Cunningham D D
CS Department of Microbiology and Molecular Genetics, University of California, Irvine, California 92717, USA.

NC AG00538 (NIA)
AG00096 (NIA)
SO JOURNAL OF NEUROSCIENCE, (1997 Jul 15) 17 (14) 5316-26.
Journal code: JDF. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199709
EW 19970904

AB Thrombin activity is a factor in acute CNS trauma and may contribute to such chronic neurodegenerative diseases as Alzheimer's disease. Thrombin is a multifunctional serine protease that catalyses the final steps in blood coagulation. However, increasing evidence indicates that thrombin also elicits a variety of cellular and inflammatory responses, including responses from neural cells. Most recently, high concentrations of thrombin were shown to cause cell death in both astrocyte and hippocampal neuron cultures. The purpose of this study was to determine the mechanisms underlying thrombin-induced cell death. Our data show that thrombin appears to cause apoptosis as evidenced by cleavage of DNA into oligonucleosomal-sized fragments, fragmentation of nuclei, and prevention of death by inhibition of protein synthesis. Synthetic peptides that directly activate the thrombin receptor also induced apoptosis, indicating that thrombin-induced cell death occurred via activation of the thrombin receptor. The signal transduction cascade involves tyrosine and serine/threonine kinases and an intact actin cytoskeleton. Additional study revealed the involvement of the small GTP-binding protein **RhoA**. Thrombin induced **RhoA** activity in both astrocytes and hippocampal **neurons**, and **inhibition** of **RhoA** activity with exoenzyme C3 attenuated cell death, indicating that thrombin activation of **RhoA** was necessary for thrombin-induced cell death. Tyrosine kinase **inhibitors** blocked thrombin induction of RhoA, indicating that tyrosine kinase activity was required upstream of RhoA. These data suggest a sequential linkage of cellular events from which we propose a model for the second messenger cascade induced by thrombin in neural cells that can lead to apoptosis.

L108 ANSWER 17 OF 31 MEDLINE
AN 97470893 MEDLINE
DN 97470893
TI Regulation of dendritic growth and remodeling by Rho, Rac, and Cdc42.
AU Threadgill R; Bobb K; Ghosh A
CS Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, USA.
SO NEURON, (1997 Sep) 19 (3) 625-34.
Journal code: AN8. ISSN: 0896-6273.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
AB The acquisition of cell type-specific morphologies is a central feature of neuronal differentiation and has important consequences for nervous system function. To begin to identify the underlying molecular mechanisms, we have explored the role of **Rho**-related GTPases in the dendritic development of cortical **neurons**. Expression of dominant negative mutants of **Rac** or **Cdc42**, the **Rho-inhibitory** molecule C3 transferase, or the GTPase-activating protein **RhoGAP** p190 causes a marked reduction in the number of primary dendrites in nonpyramidal (multipolar) **neurons** and in the number of basal dendrites in neurons with pyramidal morphologies. Conversely, the expression of constitutively active mutants of Rho, Rac, or Cdc42 leads to an increase in the number of primary and basal dendrites. In cortical cultures, as in vivo, dendritic remodeling leads to an apparent transformation from pyramidal to nonpyramidal morphologies over time. Strikingly, this shift in favor of nonpyramidal morphologies is also inhibited by the expression of dominant negative mutants of Cdc42 and Rac and by RhoGAP p190. These observations indicate that Rho, Rac, and Cdc42 play a central role in dendritic development and suggest that differential activation of Rho-related GTPases may contribute to the generation of morphological diversity in the developing cortex.

DN 98112785
TI p160 RhoA-binding kinase ROKalpha induces neurite retraction.
AU Katoh H; Aoki J; Ichikawa A; Negishi M
CS Department of Physiological Chemistry, Faculty of Pharmaceutical Sciences,
Kyoto University, Sakyo-ku, Kyoto 606, Japan.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jan 30) 273 (5) 2489-92.
Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199804
AB We previously reported that the activation of prostaglandin E receptor EP3
subtype caused neurite retraction via small GTPase Rho in the EP3B receptor-expressing PC12 cells (Katoh, H., Negishi, M., and Ichikawa, A. (1996) J. Biol. Chem. 271, 29780-29784). However, a potential downstream effector of Rho that induces neurite retraction was not identified. Here we examined the morphological effect of p160 RhoA-binding kinase ROKalpha,
a target for RhoA recently identified, on the nerve growth factor-differentiated PC12 cells. Microinjection of the catalytic domain of ROKalpha rapidly induced neurite retraction similar to that induced by microinjection of a constitutively active Rho, RhoV14, whereas microinjection of the kinase-deficient catalytic domain of ROKalpha did not induce neurite retraction. This morphological change was observed even
though C3 exoenzyme, which was known to inactivate **Rho**, had been preinjected. On the other hand, microinjection of the **Rho** -binding domain or the pleckstrin homology domain of ROKalpha **inhibited** the EP3 receptor-induced neurite retraction. These results demonstrate that ROKalpha induces neurite retraction acting downst

DN 98119818
TI Membrane targeting of p21-activated kinase 1 (PAK1) induces neurite outgrowth from PC12 cells.
AU Daniels R H; Hall P S; Bokoch G M
CS Departments of Immunology and Cell Biology, The Scripps Research Institute, 10550 North Torrey Pines Rd, La Jolla, CA 92037, USA.
NC GM44428 (NIGMS)
GM39434 (NIGMS)
SO EMBO JOURNAL, (1998 Feb 2) 17 (3) 754-64.
Journal code: EMB. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199805
AB Rho-family GTPases regulate cytoskeletal dynamics in various cell types. p21-activated kinase 1 (PAK1) is one of the downstream effectors of Rac and Cdc42 which has been implicated as a mediator of polarized cytoskeletal changes in fibroblasts. We show here that the extension of neurites induced by nerve growth factor (NGF) in the **neuronal** cell line PC12 is **inhibited** by dominant-negative Rac2 and **Cdc42**, indicating that these GTPases are required components of the NGF signaling pathway. While cytoplasmically expressed PAK1 constructs do not cause efficient neurite outgrowth from PC12 cells, targeting of these constructs to the plasma membrane via a C-terminal isoprenylation sequence induced PC12 cells to extend neurites similar to those stimulated by NGF. This effect was independent of PAK1 ser/thr kinase activity but was dependent on structural domains within both the N- and C-terminal portions of the molecule. Using these regions of PAK1 as dominant-negative inhibitors, we were able to effectively inhibit normal neurite outgrowth stimulated by NGF. Taken together with the requirement for Rac and Cdc42 in neurite outgrowth, these data suggest that PAK(s) may be acting downstream of these GTPases in a signaling system which drives polarized outgro

DN 98250713
TI Signaling pathways involved in thrombin-induced cell protection.
AU Donovan F M; Cunningham D D
CS Department of Microbiology and Molecular Genetics, University of California, Irvine, California 92717-4025, USA.
NC AG00538 (NIA)
AG00096 (NIA)
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 May 22) 273 (21) 12746-52. Journal code: HIV. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199808
AB This study examined the signal transduction pathways involved in thrombin-induced neuroprotection and compares these results with those of a similar study of thrombin-induced **neuronal** death. In thrombin-induced protection of astrocytes from hypoglycemia, pretreatment of astrocytes with tyrosine or serine/threonine kinase **inhibitors**, cytochalasin D, or exoenzyme C3, a potent inhibitor of the small GTPase **RhoA**, attenuated thrombin-induced protection. These same inhibitors were previously shown to block thrombin-induced cell death, implying a similarity in the cell death and cell-protective pathways. Biochemical assays determined that thrombin increased available RhoA activity, although more slowly and to a lesser extent than occurs in thrombin-induced cell death. A clear difference in these pathways was revealed when a time course study of thrombin-induced cell death indicated that unlike thrombin-induced protection, cells must be exposed to thrombin for >16 h to irreversibly enter the cell death pathway. Addition of lower doses of thrombin every 24 h also induced cell death. These studies indicate that exposure of cells to micromolar concentrations of thrombin alone does not induce cell death, but the continued exposure to thrombin is required. Thus the cell death and protective pathways may share initial signaling proteins, but differences in the amplitude as well as the duration of the signal may result in different final pathways.

TI Myelin and collapsin-1 induce motor neuron growth cone collapse through different pathways: inhibition of collapse by opposing mutants of rac1.

AU Kuhn T B; Brown M D; Wilcox C L; Raper J A; Bamburg J R
CS Department of Biochemistry and Molecular Biology, Colorado State University, Fort Collins, Colorado 80523, USA.

NC GM35126 (NIGMS)
GM54005 (NIGMS)
SO JOURNAL OF NEUROSCIENCE, (1999 Mar 15) 19 (6) 1965-75.
Journal code: JDF. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199906

AB Precise growth cone guidance is the consequence of a continuous reorganization of actin filament structures within filopodia and lamellipodia in response to **inhibitory** and promoting cues. The small GTPases rac1, **cdc42**, and **rhoA** are critical for regulating distinct actin structures in non-**neuronal** cells and presumably in growth cones. Collapse, a retraction of filopodia and lamellipodia, is a typical growth cone behavior on contact with inhibitory cues and is associated with depolymerization and redistribution of actin filaments. We examined whether small GTPases mediate the inhibitory properties of CNS myelin or collapsin-1, a soluble semaphorin, in chick embryonic motor neuron cultures. As demonstrated for collapsin-1, CNS myelin-evoked growth cone collapse was accompanied by a reduction of rhodamine-phalloidin staining most prominent in the growth cone periphery, suggesting actin filament disassembly. Specific mutants of small GTPases were capable of desensitizing growth cones to CNS myelin or collapsin-1. Adenoviral-mediated expression of constitutively active rac1 or rhoA abolished CNS myelin-induced collapse and allowed remarkable neurite extension on a CNS myelin substrate. In contrast, expression of dominant negative rac1 or cdc42 negated collapsin-1-induced growth cone collapse and promoted neurite outgrowth on a collapsin-1 substrate. These findings suggest that small GTPases can modulate the signaling pathways of inhibitory stimuli and, consequently, allow the manipulation of growth cone behavior. However, the fact that opposite mutants of rac1 were effective against different inhibitory stimuli speaks against a universal signaling pathway underlying growth cone collapse.

DN 99388980
TI Different roles for RhoA during neurite initiation, elongation, and regeneration in PC12 cells.
AU Sebok A; Nusser N; Debreceni B; Guo Z; Santos M F; Szeberenyi J; Tigyi G
CS Department of Physiology and Biophysics, University of Tennessee, Memphis 38163, USA.
SO JOURNAL OF NEUROCHEMISTRY, (1999 Sep) 73 (3) 949-60.
Journal code: JAV. ISSN: 0022-3042.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
AB The goal of the present study was to characterize the effects of RhoA at different stages of nerve growth factor (NGF)-induced neuronal differentiation in the PC12 model. This comparative analysis was prompted by previous studies that reported apparently opposite effects for Rho in different models of neuronal differentiation and regeneration. PC12 cells were transfected with activated V14RhoA or dominant negative N19RhoA under the control of either a constitutive or a steroid-regulated promoter. Upon exposure to NGF, V14RhoA cells continued to proliferate and did not extend neurites; however, they remained responsive to NGF, as indicated by the activation of extracellular signal-regulated kinases. This inability to differentiate was reversed by C3 toxin and activation of cyclic AMP signaling, which inactivate RhoA. N19RhoA expression led to an increase in neurite initiation and branching. In contrast, when the RhoA mutants were expressed after NGF priming, only the rate of neurite extension was altered; V14RhoA clones had neurites approximately twice as long, whereas neurites of N19RhoA cells were approximately 50% shorter than those of appropriate controls. The effects of **Rho** in neurite regeneration mimicked those observed during the initial stages of morphogenesis; activation **inhibited**, whereas inactivation promoted, neurite outgrowth. Our results indicate that **RhoA** function changes at different stages of NGF-induced **neuronal** differentiation and neurit

L1 ANSWER 1 OF 6 MEDLINE
AN 2000305288 MEDLINE
DN 20305288
TI Inhibition of Rho protein stimulates iNOS expression in rat vascular smooth muscle cells.
AU Muniyappa R; Xu R; Ram J L; Sowers J R
CS Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan 48201, USA.
SO Am J Physiol Heart Circ Physiol, (2000 Jun) 278 (6) H1762-8. Journal code: DKM. ISSN: 0363-6135.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200009
EW 20000903
AB Inducible nitric oxide synthase (iNOS) in vascular smooth muscle cells (VSMCs) is upregulated in arterial injury and plays a role in regulating VSMC proliferation and restenosis. Inflammatory cytokines [e.g., interleukin-1beta (IL-1beta)] released during vascular injury induce iNOS.

Small GTP-binding proteins of the Ras superfamily play a major role in IL-1beta-dependent signaling pathways. In this study, we examined the role

of Rho GTPases in regulating iNOS expression in VSMCs. Treatment of VSMCs with mevastatin, which inhibits isoprenylation of Rho and other small GTP-binding proteins, produced significantly higher amounts of IL-1beta-evoked NO and iNOS protein compared with control. Similarly, bacterial toxins [Toxin B from Clostridium difficile and **C3 ADP-ribosyl transferase** (**C3**) toxin
from Clostridium botulinium] that specifically inactivate Rho proteins increased NOS products (NO and citrulline) and iNOS expression. Toxin B increased the activity of iNOS promoter-reporter construct in VSMCs. Both toxins enhanced IL-1beta-stimulated iNOS expression and NO production. These data demonstrate for the first time that inhibition of Rho induces iNOS and suggest a role for Rho protein in IL-1beta-stimulated NO production in VSMCs.

L1 ANSWER 2 OF 6 MEDLINE
AN 1999339959 MEDLINE
DN 99339959
TI Phosphoinositide-dependent activation of Rho A involves partial opening of

the RhoA/Rho-GDI complex.
AU Faure J; Vignais P V; Dagher M C
CS Laboratoire de Biochimie et Biophysique des Syst`emes Integres, Departement de Biologie Moleculaire et Structurale, CEA Grenoble, France.
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1999 Jun) 262 (3) 879-89. Journal code: EMZ. ISSN: 0014-2956.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Cancer Journals; Priority Journals
EM 199910
AB Rho GTPases have two interconvertible forms and two cellular localizations. In their GTP-bound conformation, they bind to the cell membrane and are activated. In the inactive GDP-bound conformation, they associate with a cytosolic protein called GDP dissociation inhibitor (GDI). We previously reported that the RhoA component of the RhoA/Rho-GDI

complex was not accessible to the Clostridium botulinum **C3 ADP-ribosyl transferase**, unless the complex had been incubated with phosphoinositides. We show here that PtdIns, PtdIns4P, PtdIns3,4P2, PtdIns4,5P2 and PtdInsP3 enhance not only the C3-dependent ADP-ribosylation, but also the GDP/GTP exchange in the RhoA component of the prenylated RhoA/Rho-GDI complex. In contrast, in the nonprenylated RhoA/Rho-GDI complex, the levels of ADP-ribosylation and GDP/GTP exchange are of the same order as those measured on free RhoA and are not modified by phosphoinositides. In both cases, phosphoinositides partially opened, but did not fully dissociate the complex. Upon treatment of the prenylated RhoA/Rho-GDI complex with phosphoinositides, a GTP-dependent transfer to neutrophil membranes was evidenced. Using an overlay assay with the prenylated RhoA/Rho-GDI complex pretreated with PtdIns4P and labeled with [alpha32P]GTP, three membrane proteins with molecular masses between 26 and 32 kDa were radiolabeled. We conclude that in the presence of phosphoinositides, the prenylated RhoA/Rho-GDI complex partially opens, which allows RhoA to exchange GDP for GTP. The opened GTP-RhoA/Rho-GDI complex acquires the capacity to target specific membrane proteins.

L1 ANSWER 3 OF 6 MEDLINE
AN 1999225518 MEDLINE
DN 99225518
TI Phosphorylation of adducin by Rho-kinase plays a crucial role in cell motility.
AU Fukata Y; Oshiro N; Kinoshita N; Kawano Y; Matsuoka Y; Bennett V; Matsuura Y; Kaibuchi K
CS Division of Signal Transduction, Nara Institute of Science and Technology, Ikoma 630-0101, Japan.
SO JOURNAL OF CELL BIOLOGY, (1999 Apr 19) 145 (2) 347-61. Journal code: HMV. ISSN: 0021-9525.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199907
AB Adducin is a membrane skeletal protein that binds to actin filaments (F-actin) and thereby promotes the association of spectrin with F-actin to form a spectrin-actin meshwork beneath plasma membranes such as ruffling membranes. Rho-associated kinase (Rho- kinase), which is activated by the small guanosine triphosphatase Rho, phosphorylates alpha-adducin and thereby enhances the F-actin-binding activity of alpha-adducin in vitro. Here we identified the sites of phosphorylation of alpha-adducin by Rho-kinase as Thr445 and Thr480. We prepared antibody that specifically recognized alpha-adducin phosphorylated at Thr445, and found by use of this antibody that Rho-kinase phosphorylated alpha-adducin at Thr445 in COS7 cells in a Rho-dependent manner. Phosphorylated alpha-adducin accumulated in the membrane ruffling area of Madin-Darby canine kidney (MDCK) epithelial cells and the leading edge of scattering cells during the action of tetradecanoylphorbol-13-acetate (TPA) or hepatocyte growth factor (HGF). The microinjection of Botulinum **C3 ADP-ribosyl-transferase**, dominant negative Rho-kinase, or alpha-adducinT445A,T480A (substitution of Thr445 and Thr480 by Ala) inhibited the TPA-induced membrane ruffling in MDCK cells and wound-induced migration in NRK49F cells. alpha-AdducinT445D,T480D (substitution of Thr445 and Thr480 by Asp), but not alpha-adducinT445A,T480A, counteracted the inhibitory effect of the dominant negative Rho-kinase on the TPA-induced membrane ruffling in MDCK cells. Taken together, these results indicate that Rho-kinase phosphorylates alpha-adducin downstream of Rho in vivo, and that the phosphorylation of

adducin by Rho-kinase plays a crucial role in the regulation of membrane ruffling and cell motility.

L1 ANSWER 4 OF 6 MEDLINE
AN 1999038202 MEDLINE
DN 99038202
TI p21(WAF1/CIP1) is upregulated by the geranylgeranyltransferase I inhibitor GGTI-298 through a transforming growth factor beta- and Sp1-responsive element: involvement of the small GTPase rhoA.
AU Adnane J; Bizouarn F A; Qian Y; Hamilton A D; Sebti S M
CS Drug Discovery Program, H. Lee Moffitt Cancer Center, and Department of Biochemistry and Molecular Biology, University of South Florida, Tampa, Florida 33612, USA.
NC CA-67771 (NCI)
SO MOLECULAR AND CELLULAR BIOLOGY, (1998 Dec) 18 (12) 6962-70. Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199903
AB We have recently reported that the geranylgeranyltransferase I inhibitor GGTI-298 arrests human tumor cells at the G1 phase of the cell cycle and increases the protein and RNA levels of the cyclin-dependent kinase inhibitor p21(WAF1/CIP1). Here, we show that GGTI-298 acts at the transcriptional level to induce p21(WAF1/CIP1) in a human pancreatic carcinoma cell line, Panc-1. This upregulation of p21(WAF1/CIP1) promoter was selective, since GGTI-298 inhibited serum responsive element- and E2F-mediated transcription. A functional analysis of the p21(WAF1/CIP1) promoter showed that a GC-rich region located between positions -83 and -74, which contains a transforming growth factor beta-responsive element and one Sp1-binding site, is sufficient for the upregulation of p21(WAF1/CIP1) promoter by GGTI-298. Electrophoretic mobility shift assays showed a small increase in the amount of DNA-bound Sp1-Sp3 complexes. Furthermore, the analysis of Sp1 transcriptional activity in GGTI-298-treated cells by using GAL4-Sp1 chimera or Sp1-chloramphenicol acetyltransferase reporter revealed a significant increase in Sp1-mediated transcription. Moreover, GGTI-298 treatment also resulted in increased Sp1 and Sp3 phosphorylation. These results suggest that GGTI-298-mediated upregulation of p21(WAF1/CIP1) involves both an increase in the amount of DNA-bound Sp1-Sp3 and enhancement of Sp1 transcriptional activity. To identify the geranylgeranylated protein(s) involved in p21(WAF1/CIP1) transcriptional activation, we analyzed the effects of the small GTPases Rac1 and RhoA on p21(WAF1/CIP1) promoter activity. The dominant negative mutant of RhoA, but not Rac1, was able to activate p21(WAF1/CIP1). In contrast, constitutively active RhoA repressed p21(WAF1/CIP1). Accordingly, the **ADP-ribosyl transferase C3**, which specifically inhibits Rho proteins, enhanced the activity of p21(WAF1/CIP1). Taken together, these results suggest that one mechanism by which GGTI-298 upregulates p21(WAF1/CIP1) transcription is by preventing the small GTPase RhoA from repressing p21(WAF1/CIP1) induction.

L1 ANSWER 5 OF 6 MEDLINE
AN 97347435 MEDLINE
DN 97347435
TI Rho proteins play a critical role in cell migration during the early phase of mucosal restitution.
AU Santos M F; McCormack S A; Guo Z; Okolicany J; Zheng Y; Johnson L R; Tigyi

G
CS Department of Physiology and Biophysics, University of Tennessee, College of Medicine, Memphis, Tennessee 38163, USA.
NC DK 37260 (NIDDK)
SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Jul 1) 100 (1) 216-25.
Journal code: HS7. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199710
AB In the intestine, several growth factors stimulate migration of epithelial cells, contributing to the maintenance of tissue integrity. The Ras-like GTPase Rho regulates a signal transduction pathway linking growth factor receptors to the formation of actin stress fibers and focal adhesions, presumed to be important for motility. Using an in vitro wound-induced migration assay, we have examined the role of Rho GTPases in the migration of IEC-6 and Caco-2 cells, and provide evidence that the Rho GTPases play an essential role in the initial phase of mucosal wound healing. Treatment of the cells with Clostridium difficile toxins A and B, inhibitors of the Rho family GTPases inhibited migration in a dose-dependent fashion. Microinjection of the inhibitory exchange factor Rho-guanine nucleotide dissociation inhibitor (GDI), or Clostridium botulinum **C3 ADP-ribosyl transferase** (**C3**) toxin, a Rho-**ADP**-ribosylating exoenzyme, potently inhibited migration. Microinjection of RhoT19N, a dominant negative form of RhoA, or in vitro ADP-ribosylated RhoA impaired the ability of cells to migrate. Rho-GDI and C3 exoenzyme also inhibited EGF-induced migration of IEC-6 cells. These results demonstrate that Rho is required for endogenous and EGF-induced migration of small intestinal crypt cells, and that Rho proteins are essential elements of a mechanism by which growth factors induce cell migration to restitute mucosal integrity.

L1 ANSWER 6 OF 6 MEDLINE
AN 91180969 MEDLINE
DN 91180969
TI Identification of specific domains in botulinum and tetanus neurotoxins.
AU Singh B R
CS Department of Food Microbiology and Toxicology, Environmental Toxicology Center, University of Wisconsin, Madison 53706.
SO TOXICON, (1990) 28 (8) 992-6.
Journal code: VWT. ISSN: 0041-0101.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199107
AB Specific domains of botulinum and tetanus neurotoxins have been identified by computing the bias in the use of Lys over Arg in their respective polypeptide chains (E. London and C.L. Luongo, Biochem. biophys. Res. Commun. 160, 333-339, 1989). A strong bias was noted in the C-terminal domain of the light chains of both the neurotoxins (bRK', -8.0 to -12.0) suggesting that this domain could represent a 'catalytic domain' similar to that present in other dichain toxins such as diphtheria. Interestingly, this domain has a segment which has significant homology with the partial sequence of botulinum exoenzyme **C3**, and **ADP-ribosyl transferase**, implying a possible relationship with an enzymatic activity.

L8 ANSWER 4 OF 8 MEDLINE
AN 95213748 MEDLINE
DN 95213748 PubMed ID: 7699401
TI Role of growth factors in degeneration and regeneration in the central nervous system; clinical experiences with **NGF** in Parkinson's and Alzheimer's diseases.
AU Olson L; Backman L; Ebendal T; Eriksdotter-Jonhagen M; Hoffer B; Humpel C; Freedman R; Giacobini M; Meyerson B; Nordberg A; +
CS Department of Neuroscience, Karolinska Institute, Stockholm, Sweden.
NC AG04418 (NIA)
NS09199 (NINDS)
SO JOURNAL OF NEUROLOGY, **(1994 Dec)** 242 (1 Suppl 1) S12-5. Ref: 21
Journal code: 0423161. ISSN: 0340-5354.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199505
ED Entered STN: 19950510
Last Updated on STN: 19980206
Entered Medline: 19950503
AB Neurotrophin-mediated mechanisms are integral to development and maintenance of the adult central nervous system. Neurotrophin expression has been shown to change rapidly in response to many different types of neuronal stress such as excitotoxic injury, mechanical lesions, epileptogenesis and ischemia. It therefore appears as if they are not only to be regarded as target-derived trophic factors in the classical sense, but also as providers of local trophic support and neuronal protection. These discoveries suggest that neurotrophins or compounds with neurotrophin-like actions might become useful in developing new treatment strategies, not only for neurodegenerative diseases, but also for other diseases and injuries to the nervous system including **stroke**.

L8 ANSWER 5 OF 8 MEDLINE
AN 94152334 MEDLINE
DN 94152334 PubMed ID: 8109297
TI Reparative strategies in the brain: treatment strategies based on trophic factors and cell transfer techniques.
AU Olson L
CS Department of Histology and Neurobiology, Karolinska Institutet, Sweden.
NC AG04418 (NIA)
NS 09199 (NINDS)
SO ACTA NEUROCHIRURGICA. SUPPLEMENTUM, **(1993)** 58 3-7. Ref: 23
Journal code: 0140560. ISSN: 0065-1419.
CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199403
ED Entered STN: 19940330
Last Updated on STN: 20000303
Entered Medline: 19940324
AB Three reparative strategies based on transfer of genes, molecules, or cells to the central nervous system are reviewed. When neurons are already lost, they can sometimes be replaced by transfer to the target area of neurons or other cells compensating for the lost functions. This

technique is undergoing clinical trials in Parkinson's disease. Before neurons have died, it may be possible to prevent "stressed" neurons from dying, and stimulate nerve terminal ramifications from remaining neurons using treatment with neurotrophic factors. Such approaches, with an emphasis on the **NGF** family of neurotrophins and their receptors, are reviewed. Finally, advances of molecular biology techniques suggest that it should be possible to transfer genes directly into non-dividing cells of the central nervous system. The three different approaches all aim at long-lasting counteractive and reparative measures in the central nervous system. It is predicted that they have general applicability, and may become important not only in neurodegenerative diseases, but also in other common afflictions of the nervous system such as ischaemia, **stroke** and injury

L8 ANSWER 6 OF 8 MEDLINE
AN 94069614 MEDLINE
DN 94069614 PubMed ID: 8249011
TI Growth factors protect neurons against excitotoxic/ischemic damage by stabilizing calcium homeostasis.
AU Mattson M P; Cheng B
CS Sanders-Brown Research Center on Aging, University of Kentucky, Lexington 40536-0230.
NC AG05144 (NIA)
NS29001 (NINDS)
SO STROKE, **(1993 Dec)** 24 (12 Suppl) I136-40; discussion I144-5.
Journal code: 0235266. ISSN: 0039-2499.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199401
ED Entered STN: 19940201
Last Updated on STN: 20000303
Entered Medline: 19940104
AB An aberrant elevation in intraneuronal calcium levels resulting from energy failure and excitatory amino acid receptor activation is believed to play a major role in the neuronal damage and death that occur in **stroke**. We have found that several growth factors can protect cultured rat hippocampal and septal neurons and human cortical neurons from excitotoxic damage caused by glucose deprivation or hypoxia. Using the calcium indicator dye fura 2 and whole-cell patch-clamp recording, we found that glucose deprivation initially results in calcium current inhibition and a reduction in intraneuronal free calcium levels without morphological signs of cell damage. After 12 to 16 hours of glucose deprivation, a large elevation in intraneuronal calcium levels occurred that involved N-methyl-D-aspartate receptor activation and mediated the cell damage and death. Basic fibroblast growth factor (bFGF), nerve growth factor (**NGF**), and insulin-like growth factors (IGF-I and IGF-II) each prevented, in a dose-dependent manner, glucose deprivation-induced loss of calcium homeostasis and neuronal damage. The growth factors were effective to varying degrees when added up to 12 hours after the onset of glucose deprivation. **NGF**, bFGF, and IGFs also protected neurons against damage caused by exposure to a hypoxic environment. By stabilizing intraneuronal calcium levels within a window of concentrations conducive to neuronal survival, growth factors can protect neurons against the damaging effects of ischemia-like insults. Because ATP levels are expected to be reduced under ischemia-like conditions, we determined whether the growth factors would protect neurons against a more selective reduction in ATP levels.(ABSTRACT TRUNCATED AT 250 WORDS)

L7 ANSWER 1628 OF 1629 MEDLINE
AN 74255182 MEDLINE
DN 74255182 PubMed ID: 4365380
TI Mechanism of action of **nerve growth factor** and cyclic AMP on neurite **outgrowth** in embryonic chick sensory ganglia: demonstration of independent pathways of stimulation.
AU Frazier W A; Ohlendorf C E; Boyd L F; Aloe L; Johnson E M; Ferrendelli J A; Bradshaw R A
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1973 Aug) 70 (8) 2448-52.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197408
ED Entered STN: 19900310
Last Updated on STN: 19900310
Entered Medline: 19740827

L7 ANSWER 1629 OF 1629 MEDLINE
AN 69013155 MEDLINE
DN 69013155 PubMed ID: 5628756
TI **Outgrowth** of sympathetic adrenergic neurons in mice treated with a **nerve-growth factor** (NGF).
AU Olson L
SO ZEITSCHRIFT FUR ZELLFORSCHUNG UND MIKROSKOPISCHE ANATOMIE, (1967) 81 (2) 155-73.
Journal code: 7503955. ISSN: 0044-3794.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 196812
ED Entered STN: 19900101
Last Updated on STN: 19900101
Entered Medline: 19681208

L7 ANSWER 1620 OF 1629 MEDLINE
AN 76239772 MEDLINE
DN 76239772 PubMed ID: 939968
TI Morphometric analysis of rat superior cervical ganglion after axotomy and **nerve growth factor** treatment.
AU Hendry I A; Campbell J
SO JOURNAL OF NEUROCYTOLOGY, (1976 Jun) 5 (3) 351-60.
Journal code: 0364620. ISSN: 0300-4864.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197609
ED Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19760925
AB The changes in neuronal number, cell body size and nuclear size have been followed for 12 weeks after postganglionic axotomy of the rat superior cervical ganglion. Axotomy was carried out at 6 days post partum and treatment with **nerve growth factor** (NGF) was from 6-21 days. During normal development there is a 30% decrease in the number of neurons in the superior cervical ganglion; axotomy increases the loss of cells resulting in a 90% decrease by 28 days post partum. The normal decrease is prevented and the enhanced loss of cells after axotomy is decreased by administration of NGF. Thus the increased number of cells observed after NGF administration appears to be due to the survival of cells that otherwise would have degenerated. NGF causes a rapid enlargement of both the cell bodies and the nucleus in the normal and axotomized ganglia. This increase in size rapidly reverses after cessation of treatment. These changes in cell size may account for the previously observed changes in cell profile number with NGF. There is a large increase in the number of non-neuronal cells during normal development and axotomy prevents this increase. NGF treatment results in a 6 fold increase in the number of non-neuronal cells and it is suggested that these are required to support the massive fibre **outgrowth** that occurs in NGF treated ganglia. It is concluded that these results are consistent with a physiological role for NGF as the trophic substance supporting adrenergic neurons making the appropriate contact with their target cell.

L3 ANSWER 54 OF 64 MEDLINE
AN 90149401 MEDLINE
DN 90149401 PubMed ID: 2620177
TI 'Addition of nerve growth factor to the interior of a tubular prosthesis increases sensory neuron regeneration in **vivo**.
AU Da-Silva C F; Langone F
CS Departamento de Anatomia, Universidade de Sao Paulo, Brasil.
SO BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH, (1989) 22 (6) 691-4. Journal code: 8112917. ISSN: 0100-879X.
CY Brazil
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199003
ED Entered STN: 19900601
Last Updated on STN: 19980206
Entered Medline: 19900326
AB The sciatic nerve of adult mice was transected and the proximal and distal nerve stumps were sutured into a polyethylene tube. The tubes were implanted either empty, or the lumen was filled with pure collagen or a mixture of collagen/nerve growth factor (**NGF**). Six weeks later, cells in the L3-L5 dorsal root ganglia (**DRG**) were retrogradely filled with horseradish peroxidase (HRP). The data demonstrate that the addition of **NGF** to the interior of the tubular prosthesis can significantly increase the regeneration rate of sensory neurons.

L3 ANSWER 59 OF 64 MEDLINE
AN 88141353 MEDLINE
DN 88141353 PubMed ID: 2449541
TI Neuron-enriched cultures of adult rat dorsal root ganglia: establishment, characterization, survival, and neuropeptide expression in response to trophic factors.
AU Grothe C; Unsicker K
CS Department of Anatomy and Cell Biology, University of Marburg, Federal Republic of Germany.
SO JOURNAL OF NEUROSCIENCE RESEARCH, (1987) 18 (4) 539-50.
Journal code: 7600111. ISSN: 0360-4012.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198804
ED Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19880401
AB It is unknown whether adult dorsal root ganglion (**DRG**) neurons require trophic factors for their survival and maintenance of neuropeptide phenotypes. We have established and characterized neuron-enriched cultures of adult rat **DRGs** and investigated their responses to nerve growth factor (**NGF**), ciliary neuronotrophic factor (CNTF), pig brain extract (PBE, crude fraction of brain-derived neuronotrophic factor, BDNF), and laminin (LN). **DRGs** were dissected from levels C1 through L6 and dissociated and freed from myelin fragments and most satellite (S-100-immunoreactive) cells by centrifugation on Percoll and preplating. The enriched neurons, characterized by their morphology and immunoreactivity for neuron-specific enolase, constituted a population representative of the in **vivo** situation with regard to expression of substance P (SP), somatostatin (SOM), and cholecystokinin-8 (CCK) immunoreactivities. In the absence of trophic factors and using polyornithine (PORN) as a substratum, 60-70% of the neurons present initially (0.5 days) had died after 7 days. LN as a substratum did not prevent a 30% loss of neurons up to day 4.5, but it subsequently maintained **DRG** neurons at a plateau. This behavior might reflect a cotrophic effect of LN and factors provided by non-neuronal cells, whose proliferation between 4.5 and 7 days could not be prevented by addition of mitotic inhibitors of gamma-irradiation. CNTF, but not **NGF**, slightly enhanced survival at 7 days on either PORN or LN. No neuronal losses were found in non-enriched cultures or when enriched neurons were supplemented with PBE, indicating that non-neuronal cells and PBE provide factor(s) essential for adult **DRG** neuron survival. Proportions of SP-, SOM-, and CCK-immunoreactive cells were unaltered under any experimental condition, with the exception of a numerical decline in SP cells in 7-day cultures with LN, but not PORN, as the substratum. Our data, considered in the context of recent in **vivo** and vitro studies, suggest that a combination of trophic factors or an unidentified factor, rather than the established molecules **NGF**, CNTF, and BDNF, which address embryonic and neonatal **DRG** neurons, are required for the in vitro maintenance of adult **DRG** neurons.

L4 ANSWER 12 OF 65 MEDLINE
AN 97155737 MEDLINE
DN 97155737 PubMed ID: 9002392
TI Experimental neurotrophic factor therapy leads to cortical synaptic remodeling and compensates for behavioral deficits.
AU Cuello A C
CS Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada.
NC AG11903-01A1 (NIA)
SO JOURNAL OF PSYCHIATRY AND NEUROSCIENCE, **(1997 Jan)** 22 (1) 46-55.
Ref: 78
Journal code: 9107859. ISSN: 1180-4882.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199702
ED Entered STN: 19970227
Last Updated on STN: 20000303
Entered Medline: 19970212
AB This brief review discusses experimental therapy with neurotrophic factors in a model of central nervous system (**CNS**) neural atrophy and synaptic loss resulting from unilateral cortical infarctions. It discusses the trophic factor protection of the cholinergic phenotype of neurons belonging to the forebrain-to-neocortex projection, as well as the capacity of trophic therapy to elicit synaptogenesis in the cerebral cortex of adult animals. Finally, it addresses the behavioral consequences of trophic factor-induced synaptic remodeling of the neocortex in this model.

L4 ANSWER 18 OF 65 MEDLINE
AN 96427039 MEDLINE
DN 96427039 PubMed ID: 8963994
TI The effect of the platelet derived wound healing formula and the **nerve growth factor** on the experimentally injured spinal cord.
AU Hiraizumi Y; Fujimaki E; Transfeldt E E; Kawahara N; Fiegel V D; Knighton D; Sung J H
CS Department of Orthopaedic Surgery, Showa University, Tokyo, Japan.
SO SPINAL CORD, **(1996 Jul)** 34 (7) 394-402.
Journal code: 9609749. ISSN: 1362-4393.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199612
ED Entered STN: 19970128
Last Updated on STN: 19970128
Entered Medline: 19961210
AB The main purpose of this study is to investigate the effect of platelet derived wound healing formula (PDWHF) and **nerve growth factor** (**NGF**) in the treatment of experimental spinal cord injury. PDWHF is a conglomerate of growth factors which include platelet derived growth factor (PDGF), platelet derived angiogenesis factor (PDAF), transforming growth factor-beta (TGF beta) and platelet factor IV (PF4). Complete spinal cord transection was performed at T12 in rats and the treatment of the spinal cord injury was achieved by filling the dead space with type 1 collagen gel impregnated with PDWHF, or with 2.5S-**NGF**. Controls were treated with only type 1 collagen gel. Animals were sacrificed at 1, 2 or 3 months. Histopathologically, tissue autolysis and cavity formation by phagocytosis expanded 1-3 mm into the cord stumps and the volume of cavitation was less in the two treated groups. In the **NGF** group, a greater number of surviving nerve cells were observed in this region. Most of the control animals formed only thin, short axonal bundles, however, increased axonal regrowth was noted in animals treated with trophic factors, especially in the **NGF** group. The **NGF** group formed thick axonal bundles and abundant neuroma. Increased angiogenesis was observed in the collagen gel matrix and the injured spinal cord parenchyma, in the PDWHF group. Recent studies have shown that mammalian adult **CNS** possesses the ability for structural and/or functional plasticity following injury under appropriate circumstances. In this in vivo study, exogenous **NGF** appeared to induce axomal outgrowth and nerve cell survival. PDWHF produced notable angiogenesis which seemed to improve the extracellular microenvironment. This may be important for the delivery of exogenous trophic factors, nutrients and for the changes of extracellular matrices to support nerve cells and axons.

L4 ANSWER 6 OF 65 MEDLINE
AN 1998080568 MEDLINE
DN 98080568 PubMed ID: 9417824
TI Robust growth of chronically injured spinal cord axons induced by grafts of genetically modified **NGF**-secreting cells.
AU Grill R J; Blesch A; Tuszynski M H
CS Department of Neurosciences, University of California at San Diego, La Jolla, California 92093-0608, USA.
SO EXPERIMENTAL NEUROLOGY, **(1997 Dec)** 148 (2) 444-52.
Journal code: 0370712. ISSN: 0014-4886.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980130
Last Updated on STN: 20021217
Entered Medline: 19980122
AB Little spontaneous **regeneration** of axons occurs after acute and chronic injury to the **CNS**. Previously we have shown that the continuous local delivery of neurotrophic factors to the acutely injured spinal cord induces robust growth of spinal and supraspinal axons. In the present study we examined whether chronically injured axons also demonstrate significant neurotrophin responsiveness. Adult rats underwent bilateral dorsal hemisection lesions that axotomize descending supraspinal pathways, including the corticospinal, rubrospinal, and cerulospinal tracts, and ascending dorsal spinal sensory projections. One to three months later, injured rats received grafts of syngenic fibroblasts genetically modified to produce **nerve growth factor** (**NGF**). Control subjects received unmodified cell grafts or cells transduced to express the reporter gene beta-galactosidase. Three to five months after grafting, animals that received **NGF**-secreting grafts showed dense growth of putative cerulospinal axons and primary sensory axons of the dorsolateral fasciculus into the grafted lesion site. Growth from corticospinal, raphaespinal, and local motor axons was not detected. Thus, robust growth of defined populations of supraspinal and spinal axons can be elicited in chronic stages after spinal cord injury by localized, continuous transgenic delivery of neurotrophic factors.

L4 ANSWER 20 OF 65 MEDLINE
AN 96158431 MEDLINE
DN 96158431 PubMed ID: 8594213
TI Neurotrophic factors in central nervous system trauma.
AU Mocchetti I; Wrathall J R
CS Department of Cell Biology, Georgetown University School of Medicine, Washington D.C. 20007, USA.
NC NS 01675 (NINDS)
NS28130 (NINDS)
NS32671 (NINDS)
SO JOURNAL OF NEUROTRAUMA, **(1995 Oct)** 12 (5) 853-70. Ref: 186
Journal code: 8811626. ISSN: 0897-7151.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199604
ED Entered STN: 19960422
Last Updated on STN: 19960422
Entered Medline: 19960409
AB Although **regeneration** of injured neurons does not occur after trauma in the central nervous system (**CNS**), there is often significant recovery of functional capacity with time. Little is currently known about the molecular basis for such recovery, but the increased trophic activity in injured **CNS** tissue and the known properties of neurotrophic factors in neuronal growth and maintenance suggest that these polypeptides are probably involved in recovery of function. Members of the neurotrophin family, including **nerve growth factor** (**NGF**), brain-derived neurotrophic factors (BDNF), and neurotrophin 3 (NT-3), are capable of supporting survival of injured **CNS** neurons both in vitro and in vivo. They also stimulate neurite outgrowth, needed for reorganization of the injured **CNS**, and the expression of key enzymes for neurotransmitter synthesis that may need to be upregulated to compensate for reduced innervation. The effects of the neurotrophins are mediated through specific high affinity trk receptors (trk A, B, C) as well as a common low affinity receptor designated p75NGFR. Another class of neurotrophic polypeptides also provides candidate recovery-promoting molecules, the heparin-binding growth factors' acidic and basic fibroblast growth factor (aFGF, bFGF). FGFs not only sustain survival of injured neurons but also stimulate revascularization and certain glial responses to injury. Both the neurotrophins and the FGFs, as well as their respective receptors, have been shown to be upregulated after experimental **CNS** injury. Further, administration of neurotrophins or FGF has been shown to reduce the effects of experimental injury induced by axotomy, excitotoxins, and certain other neurotoxins. The cellular basis for the potential therapeutic use of neurotrophic molecules is discussed as well as new strategies to increase neurotrophic activity after **CNS** trauma based on the recently obtained information on pharmacological and molecular control of the expression of these genes.

L4 ANSWER 28 OF 65 MEDLINE
AN 95165445 MEDLINE
DN 95165445 PubMed ID: 7861441
TI **Nerve growth factor** in **CNS** repair.
AU Varon S; Conner J M
CS Department of Biology, School of Medicine, University of California, San Diego, La Jolla.
NC NS-16349 (NINDS)
NS-25407 (NINDS)
SO JOURNAL OF NEUROTRAUMA, **(1994 Oct)** 11 (5) 473-86. Ref: 56
Journal code: 8811626. ISSN: 0897-7151.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199503
ED Entered STN: 19950404
Last Updated on STN: 19950404
Entered Medline: 19950321
AB The hypothesis that neurotrophic factors play important roles in the adult central nervous system (**CNS**) has been successfully investigated in the past decade with regard to experimental and pathologic situations. Trophic roles in adult **CNS** axonal **regeneration**, on the other hand, have received much less attention. We review three groups of recent studies that demonstrate the relevance of **nerve growth factor** (**NGF**) for the **regeneration** of selected axons into adult central nervous tissue. The first group concerns a septohippocampal model where transected septal cholinergic axons are allowed to regrow into the hippocampal formation through a peripheral nerve bridge implanted into the transection lesion gap. **NGF** is required in the bridge, enhances penetration of the hippocampal tissue when infused there, and both attracts and promotes sprouting within the septum when infused in the lateral ventricle or the septal tissue itself. The second group of studies concerns the development of a spinal cord sensory **regeneration** model, where dorsal root ganglionic axons regrow into a nerve bridge placed within the dorsal spinal cord. Preliminary data indicate that **NGF** infusion rostral to the bridge once again promotes substantial penetration of the adult cord tissue by the **regenerating NGF**-sensitive fibers. In the third group of studies, attention has been shifted to the location of endogenous **NGF** in the adult rat hippocampal formation and the normal or lesion-induced occurrence of extrasomal **NGF** immunoreactivity. These regions of anchored **NGF** have the ability to attract **NGF**-sensitive growing axons and may provide opportunities to investigate local cues for final definition of terminal fields.

L4 ANSWER 43 OF 65 MEDLINE
AN 91192124 MEDLINE
DN 91192124 PubMed ID: 2013309
TI **Nerve growth factor** promotes **CNS** cholinergic axonal **regeneration** into acellular peripheral nerve grafts.
AU Hagg T; Gulati A K; Behzadian M A; Vahlsing H L; Varon S; Manthorpe M
CS Department of Biology, University of California, San Diego, La Jolla 92093.
NC NS-16349 (NINDS)
NS-24834 (NINDS)
NS-25011 (NINDS)
SO EXPERIMENTAL NEUROLOGY, **(1991 Apr)** 112 (1) 79-88.
Journal code: 0370712. ISSN: 0014-4886.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199105
ED Entered STN: 19910602
Last Updated on STN: 19910602
Entered Medline: 19910514
AB Peripheral nerve grafts promote vigorous **regeneration** of adult mammalian **CNS** axons. Elimination of nerve-associated cells by freeze-thawing abolishes this promoting quality, possibly by creating inhibitory cellular debris and/or destroying the production of stimulatory factors by living Schwann or other cells. Here, debris-free acellular peripheral nerve segments placed between the disconnected septum and the hippocampal formation acquired almost no cholinergic axons after 1 month. However, such acellular nerve grafts treated before implantation with purified beta-**nerve growth factor** (**NGF**) contained nearly as many longitudinally oriented cholinergic axons as did fresh cellular nerve grafts. These results suggest that (i) **NGF** is required for the **regeneration** of adult **CNS** cholinergic axons into nerve grafts and (ii) an important function of living cells within peripheral nerve may be the production of neuronotrophic factors such as **NGF**.

L4 ANSWER 50 OF 65 MEDLINE
AN 90376156 MEDLINE
DN 90376156 PubMed ID: 2398373
TI **Nerve growth factor** infusion into the denervated adult rat hippocampal formation promotes its cholinergic reinnervation.
AU Hagg T; Vahlsing H L; Manthorpe M; Varon S
CS Department of Biology, University of California, San Diego, La Jolla 92093.
NC NS-16349 (NINDS)
NS-25011 (NINDS)
SO JOURNAL OF NEUROSCIENCE, **(1990 Sep)** 10 (9) 3087-92.
Journal code: 8102140. ISSN: 0270-6474.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199010
ED Entered STN: 19901122
Last Updated on STN: 19901122
Entered Medline: 19901012
AB The well-documented but little-understood failure of lengthy axonal **regeneration** after injury of the adult mammalian **CNS** may be caused by an insufficient availability of local growth-promoting factors. If so, identifying and supplying the missing factors may result in better central axonal **regeneration**. This hypothesis was tested in an adult rat **CNS** model in which peripheral nerve grafts were placed into a lesion cavity between the septum and hippocampal formation. Continuous infusion of **nerve growth factor** (**NGF**) into the dorsal hippocampal tissue dramatically enhanced and accelerated the regrowth and penetration of cholinergic axons into the hippocampal formation. Thus, **NGF** can overcome the apparent resistance of the hippocampal **CNS** tissue to cholinergic reinnervation.

L3 ANSWER 2 OF 8 MEDLINE
AN 2002315776 MEDLINE
DN 22053496 PubMed ID: 12056835
TI NGF enhances sensory axon growth induced by laminin but not by the L1 cell adhesion molecule.
AU Liu Rong-Yu; Schmid Ralf-Steffen; Snider William D; Maness Patricia F
CS Neuroscience Center, University of North Carolina School of Medicine, Chapel Hill 27599-7260, USA.
NC NS26620 (NINDS)
NS31768 (NINDS)
SO MOLECULAR AND CELLULAR NEUROSCIENCES, (2002 May) 20 (1) 2-12.
Journal code: 9100095. ISSN: 1044-7431.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020612
Last Updated on STN: 20020808
Entered Medline: 20020807
AB Neurotrophins and cell adhesion molecules regulate axon guidance, but their potential coordinate interactions are not well defined. In particular, it has been difficult to define the role of signaling from different surface molecules in neurotrophin-induced axon growth because of the strong dependence of embryonic neurons on this class of molecules for survival. We have addressed this issue using Bax deficient neurons, which do not require neurotrophins for survival. The L1 neural cell adhesion molecule and laminin each supported NGF-independent axon growth of cultured sensory neurons from dorsal root ganglia of embryonic Bax(-/-) mice. However, nerve growth factor (NGF) stimulated additional axon growth of sensory neurons on laminin but not on L1 substrates. **Inhibition** of the small GTPase **RhoA** by the dominant-negative mutant **RhoA**(T19N) restored **NGF** responsiveness of axon growth on L1 to Bax(-/-) neurons. Constitutively activated **RhoA**(Q63L) did not affect axon growth on L1 but **inhibited NGF**-stimulated axon growth on laminin. Consistent with the concept that **RhoA** was downregulated by **NGF** in neurons on laminin but not L1, the **RhoA inhibitor** C2IN-C3 toxin stimulated axon growth on L1 in wild-type DRG neurons in **NGF**. These results demonstrate a novel substrate-dependent regulation of NGF-induced growth of embryonic sensory axons mediated by RhoA GTPase.

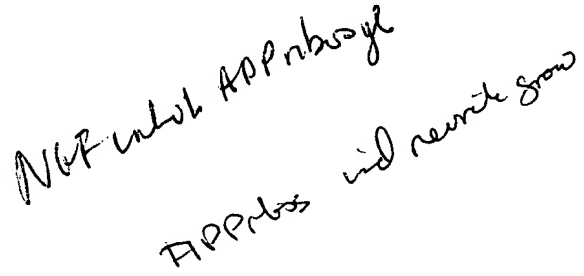
L3 ANSWER 37 OF 37 MEDLINE
AN 90142052 MEDLINE
DN 90142052 PubMed ID: 2515641
TI Botulinum **ADP-ribosyltransferase** C3: a new tool to study low molecular weight GTP-binding proteins.
AU Aktories K; Hall A
SO TRENDS IN PHARMACOLOGICAL SCIENCES, (1989 Oct) 10 (10) 415-8. Ref: 36
Journal code: 7906158. ISSN: 0165-6147.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199003
ED Entered STN: 19900328
Last Updated on STN: 20000303
Entered Medline: 19900306
AB It is well known that certain bacterial toxins, e.g. cholera and pertussis toxins, **ADP-ribosylate** eukaryotic regulatory proteins. They have become invaluable tools in the study of G protein-linked receptors. Less well appreciated is the fact that certain strains of Clostridium botulinum types C and D produce an **ADP-ribosyltransferase**, termed C3. This enzyme is structurally and functionally distinct from botulinum **neurotoxins** C1 and D. Its substrate is the 21 kDa GTP-binding protein rho. Klaus Aktories and Alan Hall explain why C3 is now an important tool in analysing the regulatory **function** of the ras-related protein **rho**.

L4 ANSWER 33 OF 35 MEDLINE
AN 94321436 MEDLINE
DN 94321436 PubMed ID: 8045941
TI Inhibition of lysophosphatidate- and thrombin-induced neurite retraction and neuronal cell rounding by ADP ribosylation of the small GTP-binding protein Rho.
AU Jalink K; van Corven E J; Hengeveld T; Morii N; Narumiya S; Moolenaar W H
CS Division of Cellular Biochemistry, The Netherlands Cancer Institute, Amsterdam.
SO JOURNAL OF CELL BIOLOGY, (1994 Aug) 126 (3) 801-10.
Journal code: 0375356. ISSN: 0021-9525.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199408
ED Entered STN: 19940909
Last Updated on STN: 20000303
Entered Medline: 19940826
AB Addition of the bioactive phospholipid lysophosphatidic acid (LPA) or a thrombin receptor-activating peptide (TRP) to serum-starved N1E-115 or NG108-15 **neuronal** cells causes rapid **growth** cone collapse, **neurite** retraction, and transient rounding of the cell body. These shape changes appear to be driven by receptor-mediated contraction of the cortical actomyosin system independent of classic second messengers. Treatment of the cells with Clostridium botulinum C3 exoenzyme, which ADP-ribosylates and thereby inactivates the **Rho** small GTP-binding protein, **inhibits** LPA- and TRP-induced force generation and subsequent shape changes. C3 also inhibits LPA-induced neurite retraction in PC12 cells. Biochemical analysis reveals that the ADP-ribosylated substrate is RhoA. Prolonged C3 treatment of cells maintained in 10% serum induces the phenotype of serum-starved cells, with initial cell flattening being followed by **neurite outgrowth**; such C3-differentiated cells fail to retract their **neurites** in response to agonists. We conclude that RhoA is essential for receptor-mediated force generation and ensuing neurite retraction in N1E-115 and PC12 cells, and that inactivation of RhoA by ADP-ribosylation abolishes actomyosin contractility and promotes **neurite outgrowth**.

L4 ANSWER 34 OF 35 MEDLINE
AN 93176163 MEDLINE
DN 93176163 PubMed ID: 8439316
TI Evidence for an indirect effect of **nerve growth** factor (NGF) on the ADP-ribosylation of a 22 kDa rho-like protein in PC12 cells.
AU Takahashi H; Guroff G
CS Section on Growth Factors, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD 20892.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1993 Feb 15) 190 (3) 1156-62.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199303
ED Entered STN: 19930402
Last Updated on STN: 20000303
Entered Medline: 19930323
AB EDIN catalyzes the ADP-ribosylation of a 22 kDa protein, probably related to rho, in permeabilized PC12 cells in a time- and dose-dependent manner. Pre-treatment of the cells with **nerve growth** factor

inhibits this EDIN-catalyzed ADP-ribosylation, both in vitro and in vivo. This inhibition is largely prevented by the addition of K-252a. **Nerve growth** factor itself causes neither ADP-ribosylation nor phosphorylation of this 22 kDa protein. These results suggest that the ADP-ribosylation of the **rho** protein is **inhibited**, albeit indirectly, by **nerve growth** factor treatment.

L4 ANSWER 35 OF 35 MEDLINE
AN 90179760 MEDLINE
DN 90179760 PubMed ID: 2106882
TI ADP-ribosylation of the **rho**/rac proteins induces **growth inhibition, neurite outgrowth** and acetylcholine esterase in cultured PC-12 cells.
AU Nishiki T; Narumiya S; Morii N; Yamamoto M; Fujiwara M; Kamata Y; Sakaguchi G; Kozaki S
CS Department of Pharmacology, Kyoto University Faculty of Medicine, Japan.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1990 Feb 28) 167 (1) 265-72.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199004
ED Entered STN: 19900601
Last Updated on STN: 20000303
Entered Medline: 19900402
AB Botulinum ADP-ribosyltransferase C3 (C3 exoenzyme) was purified to homogeneity and added to cultured rat pheochromocytoma PC-12 cells. Incubation with this exoenzyme caused inhibition of cell **growth** and induced **neurites** as well as acetylcholine esterase in these cells. These changes were dependent on the amount of the enzyme added to the culture, which correlated with the in situ ADP-ribosylation of the rho/rac proteins in the cells. Preincubation with a specific anti-C3 exoenzyme monoclonal antibody inhibited both the ADP-ribosyltransferase activity and the neurite-inducing activity of the enzyme preparation. These results suggest that C3 exoenzyme affected the cellular function of the rho/rac proteins by ADP-ribosylation to induce these changes in the cells.



L3 ANSWER 6 OF 8 MEDLINE
AN 1999321922 MEDLINE
DN 99321922 PubMed ID: 10391936
TI The myotonic dystrophy kinase-related Cdc42-binding kinase is involved in the regulation of neurite outgrowth in PC12 cells.
AU Chen X Q; Tan I; Leung T; Lim L
CS Glaxo-IMCB Group, Institute of Molecular and Cell Biology, Singapore 117609, Singapore.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Jul 9) 274 (28) 19901-5.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-AA197266
EM 199908
ED Entered STN: 19990816
Last Updated on STN: 20020420
Entered Medline: 19990805
AB The myotonic dystrophy kinase-related Cdc42-binding kinase (MRCKalpha) has been implicated in the morphological activities of Cdc42 in nonneural cells. Both MRCKalpha and the kinase-related Rho-binding kinase (ROKalpha) are involved in nonmuscle myosin light-chain phosphorylation and associated actin cytoskeleton reorganization. We now show that in PC12 cells, overexpression of the kinase domain of MRCKalpha and ROKalpha resulted in retraction of neurites formed on nerve growth factor (NGF) treatment, as observed with RhoA. However, introduction of kinase-dead MRCKalpha did not result in **NGF**-independent neurite outgrowth as observed with dominant negative kinase-dead ROKalpha or the **Rho inhibitor** C3. Neurite outgrowth induced by NGF or kinase-dead ROKalpha was inhibited by dominant negative Cdc42(N17), Rac1(N17), and the Src homology 3 domain of c-Crk, indicating the participation of common downstream components. Neurite outgrowth induced by either agent was blocked by kinase-dead MRCKalpha lacking the p21-binding domain or by a minimal C-terminal regulatory region consisting of the cysteine-rich domain/pleckstrin homology domain plus a region with homology to citron. The latter region alone was an effective blocker of NGF-induced outgrowth. These results suggest that although ROKalpha is involved in neurite retraction promoted by RhoA, the related MRCKalpha is conversely involved in neurite outgrowth promoted by Cdc42 and Rac.